Flint (A,)

Experimental Researches
into a
new excretory function of the liver

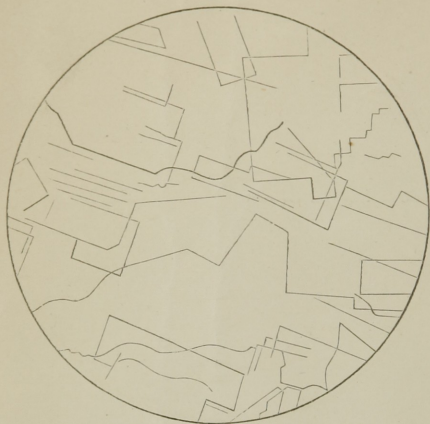+   +   +   +   +   +   +

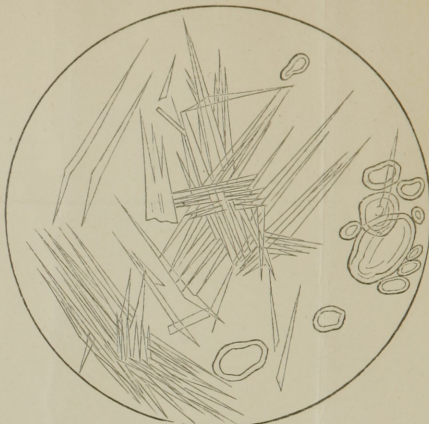Flint A.
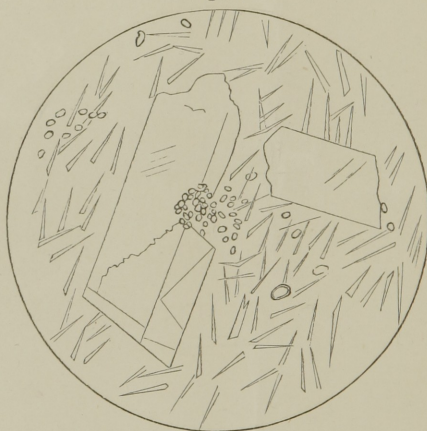
PLATE II.

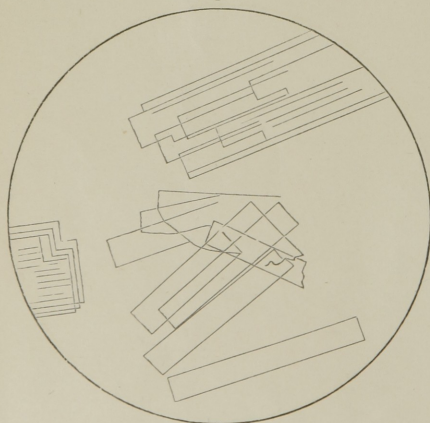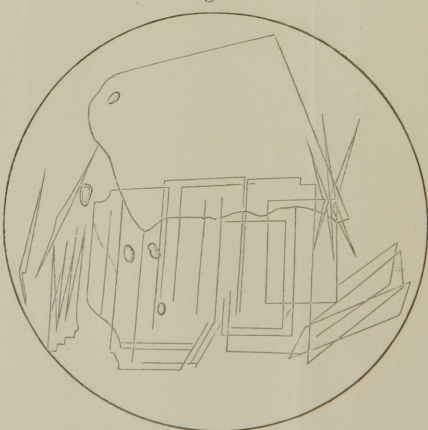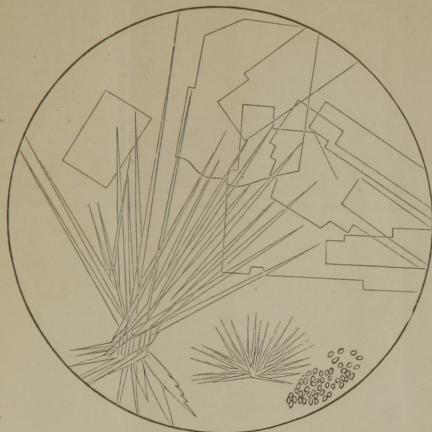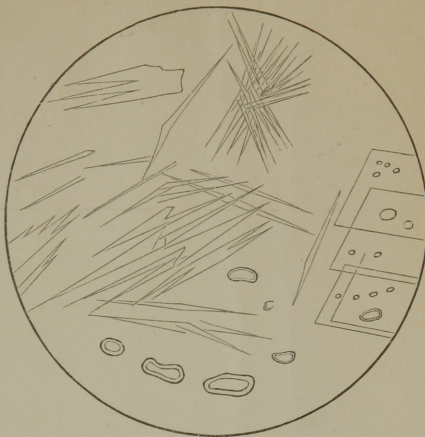Am. Journ. Med. Sci., vol. xliv.

Fig. 1.

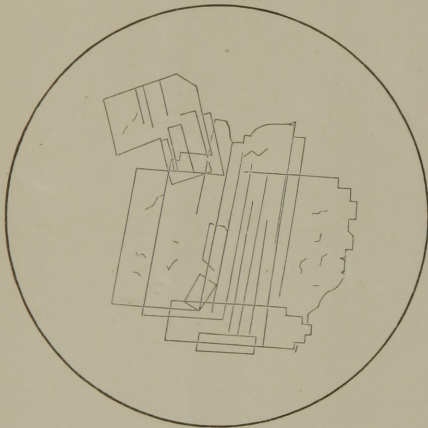Fig. 2.

Fig 3.

Fig. 4.

Fig. 5.
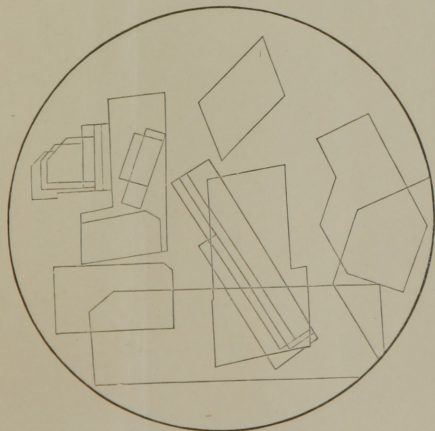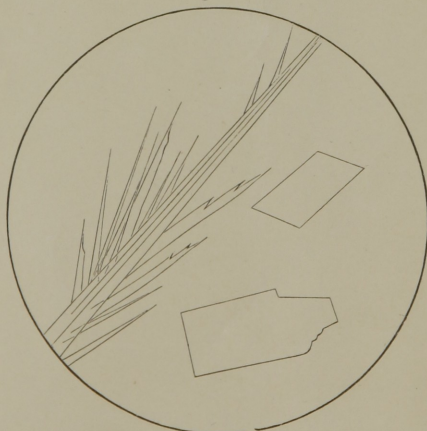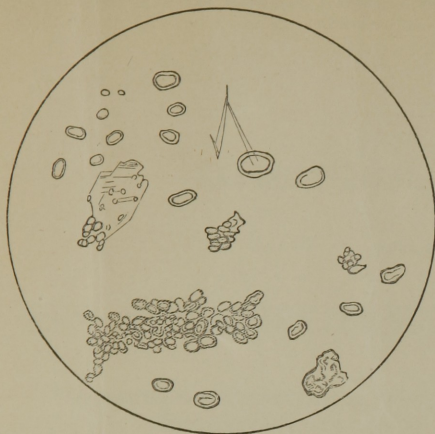
PLATE III.

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 9.

Fig. 10.
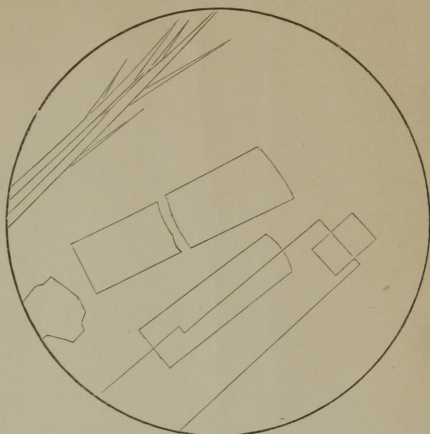
PLATE IV.

Fig. 11.

Fig. 12.

Fig. 13.
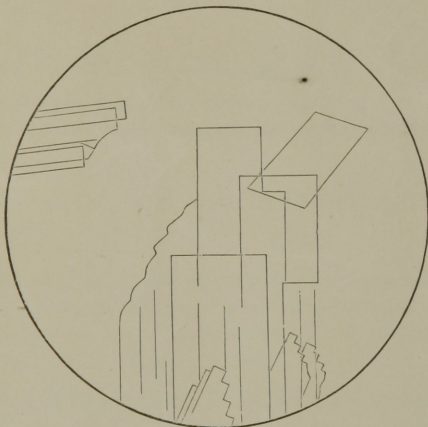
Fig. 14.
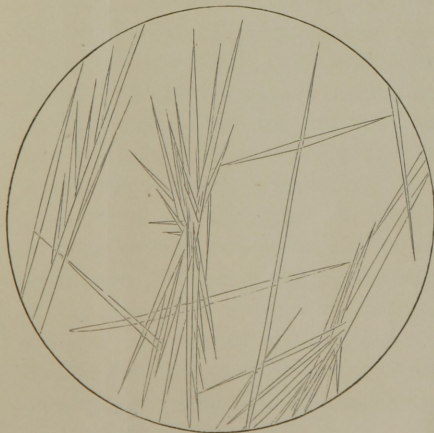
Fig. 15.
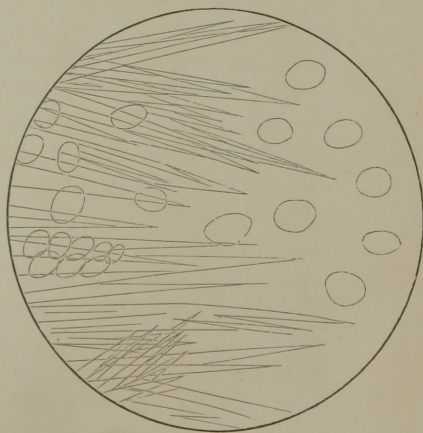
EXPERIMENTAL RESEARCHES

INTO A

NEW EXCRETORY FUNCTION OF THE LIVER;

CONSISTING IN THE REMOVAL OF CHOLESTERINE FROM THE BLOOD, AND ITS
DISCHARGE FROM THE BODY IN THE FORM OF STERCORINE.
(THE SEROLINE OF BOUDET.)

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ILLUSTRATED BY THREE PLATES CONTAINING FIFTEEN FIGURES.

"*La Cholesterine du sang est elle un de ces produits destinés à être expulsés de l'économie, et, par conséquent, dépourvus d'action immédiate sur l'économie elle même? Sa destination est tout à fait inconnue.*" Traité de Physiologie, par F. A. Longet. Paris, 1861. Tome i. p. 488.

THIS sentence, which is taken from the most elaborate treatise on physiology in any language, published at the centre of physiological science, in 1861, expresses the state of our knowledge with regard to the function of cholesterine. Cholesterine was discovered in 1782, by Poulletier de la Salle, in biliary calculi, and was detected upwards of thirty years ago in the blood by Denis; but since then, with the exception of researches of a purely chemical nature into its properties, our knowledge with regard to it has not advanced. Its chemical history even, is far from perfect; while its physiological history is unknown. In 1833 Boudet discovered a substance in the blood which he called Seroline; a principle having many characters in common with cholesterine, but heretofore interesting merely as a curious proximate principle, found in excessively minute quantities in the serum of the blood only (whence its name); too minute, indeed, for ultimate analysis. Its function was as obscure as that of cholesterine. In examining the literature of these two substances, we find that cholesterine is frequently not treated of in systematic works on physiology. Seroline is sel-

dom even mentioned. Their function has been so obscure and apparently so unimportant, that theories with regard to it have not been advanced, and the highest chemical authorities, in speaking of their office in the economy, simply say of one, as of the other, that it is unknown. In the *Chimie Anatomique*, by Robin and Verdeil, we find cholesterine summed up in these words:—

"*Le rôle physiologique qu'elle remplit dans l'économie est également inconnu.*"

Of seroline, the same authors say :—

"*On ne sait pas comment se forme la séroline, ni quel est son rôle physiologique.*"

Though the physiology of these substances is thus obscure, though chemistry has thus far done but little for their history, and physiology nothing, certain facts with relation to them would seem to indicate that they are not unimportant in the economy. Cholesterine is found in the blood, bile, liver, nervous matter, crystalline lens, meconium (not in the feces, as incorrectly stated by authors), besides in a number of morbid products. It is found in these situations *constantly;* it appears in the blood as soon as that fluid is found, and continues to the end of life. Its quantity in the blood is increased in certain diseased conditions, and diminished in others. Seroline has been said to exist constantly in the blood, though, till now, it has never been discovered in any other situation. It, like cholesterine, is a constant principle, they having many chemical characters in common. Their function is definite ; it is important ; and, if the writer do not exaggerate this importance in the enthusiasm of exploring a hitherto absolutely uncultivated field, a knowledge of the functions of these substances will be of incalculable value to the practical physician ; and the path thus opened by physiology will lead to a great field for pathological inquiry. *What the discovery of the function of urea has done for diseases which now come under the head of uremia, the discovery of the function of Cholesterine may do for the obscure diseases which may hereafter be classed under the head of Cholesteremia.*

It is not surprising that the function of substances—which have been isolated with great difficulty, *which have never been found in any of the excretions,* which exist in quantity so small, that their investigation seemed to belong especially to the chemist, physiologists having been discouraged, perhaps, from studying them—should be thus obscure. But it is surprising that that important fluid, the bile, the product of the largest gland in the economy, and the one most constantly found in the animal scale, should be so little understood. This has been regarded by some as a simple excrement, and by others as not an excrementitious, but a digestive fluid, and so much labour has been expended by physiologists in endeavours to settle this point, that no one has pretended to give an account of its excre-

mentitious function, if it have any, and researches into its digestive function have left us almost entirely in the dark. Blondlot reported an observation on a dog which lived for five years with a biliary fistula diverting, as it is stated, all the bile from the intestines and discharging it from the body. The animal presented no untoward symptoms, died a natural death, no bile found its way into the intestines, but it was all discharged. According to this observation, the bile would appear to be purely an excrement. Schwann, and Bidder and Schmidt, in a large number of experiments, never succeeded in keeping a dog operated on in this way for more than a few weeks; they all died with evidences of inanition. The bile, according to these observations, is concerned chiefly in nutrition; and as it is poured into the upper part of the digestive tube, it is important, probably, in digestion. But Bidder and Schmidt do not satisfy us what its digestive function is; nor does Blondlot say what principle is excreted by it, nor what would be the result of its suppression.

Aside from a few isolated facts, interesting enough, but indicating nothing definite, this is all we know of the function of the bile. But what physiologist does not feel this hiatus in his science; or what practical physician does not feel and know the importance of the function of the bile! It needs no inquiry into natural history, showing the universality, almost, of the liver in the animal scale, to impress upon the physician at the bedside the importance of the bile. A patient is suffering under an obscure ailment, which he may call biliousness or derangement of the liver, and which, in some unexplained way, is relieved by a mercurial purge. The practitioner knows that the bile-secreting function of the liver is important, but does not learn it from the physiologist. Every practitioner must feel that the liver has a function which must be explained him by the physiologist, before he can avoid treating a large class of diseases empirically.

The bile has an important excretory function, which is liable to many disorders; and this function the writer hopes to be able, in the present article, to describe.

It will be seen by the preceding remarks that the physiological history of the bile remains to be written. The subject is too interesting and important not to engage the mind of the experimental physiologist. It is difficult at first sight to harmonize statements, to which reference has just been made, of experimenters, equally entitled to consideration, which are diametrically opposed. But of course the philosophical method of studying the bile is first to settle whether it be excrementitious or recrementitious. If the former, what substance is excreted, and where is it formed? If the latter, what function does it perform in any of the processes of nutrition. With the view to harmonize, if possible, in my own mind, the opposite statements of Bidder and Schmidt, and Blondlot, I attempted some time ago to establish biliary fistulæ in dogs. The first experiments were made in New Orleans in the winter of 1860–61; but were all of them unsuc-

cessful, no animal surviving the operation more than three days. The experiments were discontinued at that time, but were renewed in the winter of 1861–62 at the Bellevue Hospital Medical College. After a number of trials which were no more successful than those made the previous winter, I succeeded in performing the operation with considerable rapidity and with very little disturbance of the abdominal organs, and in one animal the success was complete.

Exp. 1. The operation was performed by making an incision into the abdomen in the median line just below the ensiform cartilage, about three inches in length. The edge of the liver was carefully raised, the bile duct isolated, and two ligatures applied, one next the duodenum and the other near the junction of the ductus choledochus with the cystic duct, the intermediate portion being excised. The fundus of the gall-bladder was then drawn to the upper part of the wound, an incision made in it of about an inch in length, the bile evacuated, and the edges attached to the skin by points of the interrupted suture. The wound was then carefully closed around the opening into the gall-bladder.

This is nearly the proceeding recommended by Blondlot, who prefers, however, to operate while the animal is fasting, as the gall-bladder is then distended and can be more easily found. I have preferred to operate after feeding, when the gall-bladder is comparatively empty, as there is no great difficulty in finding it, and in evacuating its contents less bile is apt to find its way into the peritoneal cavity, which is one of the causes of the intense peritonitis which follows this operation.

The animal ate well the day after the operation, the bile flowed freely from the fistula and was entirely cut off from the intestine, as shown by post-mortem examination. No symptoms supervened except those produced by the diversion of the bile from its normal course. This operation was performed on the 15th of November, 1861, and the animal lived thirty-eight days.

In no observation that I have found recorded has the animal been so free from inflammation consequent upon so serious an operation; and this seemed a most favourable opportunity of determining whether an animal could live with the bile shut off from the intestinal tube and discharged by a fistula. In this case the animal gradually lost flesh and strength, his appetite becoming voracious, until finally he died of inanition; the observation agreeing in every important particular with the experiments of Schwann, and Bidder and Schmidt.

Exp. 2. This experiment was undertaken to ascertain, if possible, the entire quantity of bile secreted in the twenty-four hours. A fistula was made into the ductus communis choledochus, the duct being divided and a silver tube introduced. The experiment did not succeed in the point of view in which it was undertaken, and about forty-eight hours after the operation, the tube dropped out. After the removal of the tube the bile ceased to flow externally, and the animal did not appear to suffer any bad effects from the experiment. Thirty days after the operation, the animal having entirely recovered, he was killed by section of the medulla oblongata, and the parts carefully examined. The post-mortem examination I transcribe from my note book.

"On post-mortem examination the liver was found adherent to the dia-

phragm over the greater part of its convex surface. There were evidences of limited inflammation over the duodenum. The liver itself was normal. Upon opening the duodenum, the papilla which marks the opening of the ductus communis choledochus was normal in appearance. A small silver stilet was introduced into the duct. *For a long time it was impossible to find any communication between the upper part of the duct and the intestine; but at last, after patient searching (knowing that no bile was discharged from the body and that it was absolutely certain that a communication existed with the duodenum), a communication was found.* In Blondlot's case there probably was a communication re-established which escaped his observation."

In the remarkable observation reported by Blondlot, in which the animal survived for so long a period, the success is attributed to the fact that the dog was prevented from licking the bile as it flowed from the fistula, Blondlot stating that as soon as the animal was prevented from licking the bile, nutrition began to improve. Anxious to carry out all the precautions which had been adopted, I so muzzled the animal in Exp. 1, covering the lower part of the muzzle with oiled silk, that it was impossible for him to swallow a drop of the bile. This muzzle was kept on till the death of the animal, but the proceeding had no effect on his nutrition. The bile flowed so freely from the fistula that all the lower part of the animal was covered with it. It was not, however, until I made the post-mortem examination in the second experiment that I was able to see the difficulty which I had experienced in harmonizing the observations of the different experimenters I have quoted. In the lower animals—in dogs, at least—ducts have a remarkable tendency to re-establish themselves. Any one who has operated much upon the glands can hardly fail to have noticed this fact. The pancreatic duct, for example, after having been divided and a tube introduced, becomes invariably re-established after the simple removal or dropping out of the tube. It was so with Exp. 2, in which the tube dropped out of the bile duct. The duct undoubtedly became re-established, for no bile flowed externally for nearly a month, the animal enjoying perfect health, and the fluid necessarily being emptied into the intestine; yet it was with the greatest difficulty that the communication could be found with the probe, and it was only after long searching, knowing that there must be a communication, that it was discovered at all. Taking into consideration the great difficulty I had in finding the passage in this instance, and after having carefully examined the case reported by Blondlot, I have concluded that a communication existed in his experiment which escaped observation, but by means of which a large quantity of bile found its way into the intestine.[1]

[1] An account of this experiment is to be found in an article entitled *"Essai sur les Fonctions du Foi et de ses annexes par N. Blondlot."* 1846. The post-mortem examination of the animal, made more than five years after the establishment of the fistula, was published in a little memoir complementary to the preceding, entitled *"Inutilité de la Bile dans La Digestion."* 1851. It was not contemplated to

With regard to the digestive function of the bile, it is sufficient to state here that the experiments which I have made on this subject have led me to believe that this fluid has an important office in connection with the function of digestion—one, indeed, which is essential to life. The nature of its office, however, is not understood, and can only be settled by a long and carefully executed series of experimental researches which would probably involve the whole subject of digestion. This I hope to be able to present in another paper. There is, however, another function of the bile entirely distinct from the preceding. It is the separation from the blood of the cholesterine, an excrementitious substance, which is formed by the destructive assimilation of certain tissues of the body. Though not discharged from the body as cholesterine, it being first changed into another substance, it is separated in that form from the blood and poured into the intestine by the ductus communis choledochus. This new excretory function of the bile will form a great part of the subject of this paper; the recrementitious function, which is necessary to complete the physiological history of this fluid, being deferred.

We will find the cholesterine to be the most important excrement separated by the liver, as the urea is the most important one separated by the kidneys; and the study of this substance will necessarily involve the depurative function of the liver. I will therefore begin with the cholesterine, and endeavour to show where it is formed in the economy, by following the blood in its passage through various organs. This will necessarily involve a description of the chemical processes which have been employed in its extraction. I will then endeavour to show where the cholesterine is removed from the blood, by the same method of investigation. The next step will be to follow it out of the body, and study the change which it undergoes in its passage through the alimentary canal. Having described the process of formation in the tissues, separation from the blood by the liver, and final discharge from the body, I will endeavour to show, finally, the effects of interruption of this function of the liver upon the economy. This will lead us into pathology, and a host of diseases will arise which may be dependent on a disturbance of the excretory function of the liver. We will be enabled to draw the line more closely between conditions in which there is resorption simply of the innocuous colouring matter of the bile, and those diseases in which there is a failure to separate the excrements from the blood. These conditions, it is well known, are widely different as to gravity, and the distinction between them is of great importance. The latter condition, characterized by the retention of cholesterine in the blood, will be treated of under the name of *Cholesteremia*.

CHOLESTERINE.

Chemical characters.—Cholesterine is a non-nitrogenized substance, having all the properties of the fats, excepting that of saponification with the alkalies. Its chemical formula is usually given as $C^{25}H^{22}O$. It belongs to a class of fatty substances which are non-saponifiable, which have been grouped by Lehmann under the name of lipoids. This class is composed of cholesterine and seroline, which are animal substances; castorine, from the *castoreum*, and ambrein, from amber. To this he adds a substance discovered in a uterine tumour by Busch, called inosterine. Cholesterine is neutral, inodorous, crystallizable, insoluble in water, soluble in ether, very soluble in hot alcohol, though sparingly soluble in cold. It burns with a bright flame, but is not attacked by the alkalies, even after prolonged boiling. When treated with strong sulphuric acid, it strikes a peculiar red colour, which is mentioned by some as characteristic of cholesterine. I have found that it possesses this character in common with seroline.[1]

Forms of its crystals.—Cholesterine may easily and certainly be recognized by the form of its crystals, the characters of which can be made out by means of the microscope. They are rectangular or rhomboidal, exceedingly thin and transparent, of variable size, with distinct and generally regular borders, and frequently arranged in layers with the borders of the lower ones showing through those which are superimposed. This arrangement of the crystals takes place when the cholesterine is present in considerable quantity. In pathological specimens they generally are few in number, and isolated. The plates of cholesterine are frequently marked by a cleavage at one corner, the lines running parallel to the borders; frequently they are broken, and the line of fracture is generally undulating. Lehmann attaches a great deal of importance to measurements of the angles of the rhomboid; according to this author, the obtuse angles are 100° 30′, and the acute 79° 30′. I have lately examined a great number of specimens of cholesterine, extracted from the blood, bile, brain, liver, and occurring in tumours, and am confident that the crystals have no definite angle. Frequently the plates are rectangular, and sometimes almost lozenge-shaped. It is by the transparency of the plates, the parallelism of their borders, and their tendency to break in parallel lines, that we recognize them as formed of cholesterine. Lehmann seems to consider the tablets of this substance as regular crystals, having invariable angles. From examination during crystallization, I am disposed to think that they are not crystals, but fragments of micaceous sheets, which, from their extreme tenuity, are easily broken. In examining a specimen from the meconium, which I extracted with hot alcohol, I was able to see a transparent film forming on the surface of the

[1] This reaction of the seroline is mentioned by Bérard, in the " *Cours de Physiologie*," tome iii. p. 117.

alcohol soon after it cooled; this, on microscopic examination, *in situ*, disturbing the fluid as little as possible, was found to be marked by long parallel lines. When the fluid had partially evaporated, it became broken and took the form of the ordinary crystals of cholesterine, but they were larger and more regular. The beauty of the tablets at this stage could not be adequately represented. They were exceedingly thin, and regularly divided into delicate plates, with the characteristic corner cleavages of the cholesterine; and, as the focus of the instrument was changed, new layers, with different arrangement, were brought into view. I have attempted to give an idea of the form of these tablets in Fig. 1; but it is, of course, impossible to represent their pale, but beautifully distinct borders. As has been remarked by Robin, the borders of these crystals can be but imperfectly imitated by a line; there is no line in the object itself, but the edge shows where the tablet ceases. (See Fig. 1.)

The crystals are generally colourless, but when present in coloured fluids, may take a yellowish tint, or even become very dark. They may still be recognized, however, by the characters of form just described.

Crystals of cholesterine melt at 293° Fahr., but are formed again when the temperature falls below that point. According to Lehmann, they may be distilled *in vacuo* at 680° without decomposition. The determination of the fusing point is one of the means of distinguishing it from seroline, which fuses at 90° 8′.

Situation of the cholesterine.—Most authors state that the cholesterine is found in the bile, blood, liver, brain and nerves, crystalline lens, meconium, and the fecal matter. I have found the cholesterine in all these situations invariably, excepting the feces, where it was seen but once after a number of examinations; and in studying the works of those who have investigated this substance, I can find no one who has found it in the normal feces. It is found in large quantities in the meconium, from which, perhaps, it is most easily extracted in a state of purity, and has been extracted from the feces of animals in a state of hibernation; but though it may occasionally be found in the feces in disease, and in animals after long fasting, I am confident that it never occurs in the ordinary conditions. The analysis of the fecal matter is so unattractive, that it has been very much neglected by chemists; and until a few years ago, when an elaborate analysis was made by Marcet, to which reference will hereafter be made, the analyses of Berzelius formed nearly all our data on this subject. Cholesterine forms the greater part of biliary calculi, which indeed consist generally of nothing but cholesterine, colouring matter, and mucus. It is found in a large number of morbid deposits. Few cases of cancer are examined without discovering tablets of cholesterine. It is very abundant in encysted tumours. According to Robin, atheromatous deposits, which are found in the middle coats of the arteries, are often composed of cholesterine. It sometimes forms distinct tumours or deposits in the substance of the brain.

I lately had an opportunity of examining a tumour from the brain, at the Bellevue Hospital, which consisted of nearly pure cholesterine. It has often been found in the fluid of hydrocele, in the fluid of ovarian cysts, in crude tubercle, in epithelial tumours, and in pus. The proportion in which it exists in the fluids of the body is very small. I have made a number of quantitative analyses of the blood, the results of which I give in the following table, with some of the analyses which have been made for this substance. I also give the quantity which I have found in the other situations in which it is found. The variations in different parts of the circulation and in diseased conditions will be given in another table. The quantity in the brain and crystalline lens has, I believe, never before been estimated:—

Table of Quantity of Cholesterine in various Situations.

Situation.	Observer.	Quantity examined.	Cholesterine per 1,000 pts.
Venous blood (male)	Becquerel and Rodier.		0.090
Do. (female)	Becquerel and Rodier.	*grains.*	0.090
Do. (male æt. 35)	A. Flint, Jr.	312.083	0.445
Do. (male æt. 22)	A. Flint, Jr.	187.843	0.658
Do. (male æt. 24)	A. Flint, Jr.	102.680	0.751
Bile (human)	Frerichs.		1.600
Do. (normal of ox)	Berzelius.		1.000
Do. (human)	A. Flint, Jr.	224.588	0.618
Meconium.	Simon.		160.000
Do.	A. Flint, Jr.	170.541	6.245
Brain (human)	A. Flint, Jr.	159.753	7.729
Do. do.	A. Flint, Jr.	150.881	11.456
Crystalline lens (ox)[1]	A. Flint, Jr.	135.020	0.907

Form under which the cholesterine exists in the organism.—In the fluids of the body cholesterine exists in a state of solution, but by virtue of what constituents it is held in solution, is not entirely settled. It is stated that the biliary salts have the power of holding it in solution in the bile, and that the small amount of fatty acids which are contained in the blood hold it in solution in that fluid, but direct experiments on this point are wanting. In the nervous substance and in the crystalline lens it is united "*molecule à molecule*" to the other elements which go to make up these tissues. After it is discharged into the intestinal canal, when it is not changed into stercorine, it is to be found in a crystalline form, as in the meconium, and in the feces of animals in a state of hibernation. In pathological fluids and in tumours, it is found in a crystalline form, and may be detected by microscopic examination.

Process for the extraction of cholesterine.—Without describing the processes which have been employed by other observers for the extraction of cholesterine from the blood, bile, and various tissues of the body, I will confine myself to a description of the process which I have found most

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[1] In this examination four fresh crystalline lenses of the ox were used.

convenient to employ in the analyses I have made for this substance. In analyses of gall-stones the process is very simple; all that is necessary being to pulverize the mass, and extract it with boiling alcohol; filter the solution while hot, the cholesterine being deposited on cooling. If the crystals be coloured, they may be redissolved, and filtered through animal charcoal. This is the proceeding employed by Poulletier de la Salle, Fourcroy, and Chevreul. It is only when this substance is mixed with fatty matters, that its isolation is a matter of any difficulty. In extracting cholesterine from the blood, I have operated on both the serum and clot, and in this way have been able to demonstrate it in greater quantities in this fluid than has been observed by others, who have employed only the serum. The following is the process for quantitative analysis, which I determined upon after a number of experiments.

The blood, bile, or brain, as the case may be, is first carefully weighed, then evaporated to dryness over a water-bath, and carefully pulverized in an agate mortar, so as to collect every particle. The powder is then treated with ether, in the proportion of about a fluidounce for every hundred grains of the original weight, for from twelve to twenty-four hours, agitating the mixture occasionally. The ether is then separated by filtration, throwing a little fresh ether on the filter so as to wash through every trace of the fat, and the solution set aside to evaporate.[1] If the fluid, especially the blood, have been carefully dried and pulverized, when the ether is added it divides it into a very fine powder, and penetrates every part. After the ether has evaporated, the residue is extracted with boiling alcohol in the proportion of about a fluidrachm for every hundred grains of the original weight of the specimen, filtered, while hot, into a watch-glass, and allowed to evaporate spontaneously. To keep the fluid hot while filtering, the whole apparatus may be placed in the chamber of a large water-bath, or, as the filtration is generally rapid, the funnel may be warmed by plunging it into hot water, or steaming it, taking care that it be carefully wiped. We now have the cholesterine mixed with a certain quantity of saponifiable fat. After the fluid has evaporated, we can see the cholesterine crystallized in the watch-glass, mingled with masses of fat. This we remove by saponification with an alkali ; and for this purpose, we add a moderately strong solution of caustic potash, which we allow to remain in contact with the residue for from one to two hours. If much fat be present, it is best to subject the mixture to a temperature a little below the boiling point; but in analyses of the blood, this is not necessary. The mixture is then to be largely diluted with distilled water, thrown upon a small filter, and thoroughly washed till the solution which passes through is neutral. We then dry the filter, and fill it up with ether, which, in pass-

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[1] The ether may be preserved by distillation, instead of allowing it to evaporate, but with the small quantity usually employed this is hardly worth while.

ing through, dissolves out the cholesterine. The ether is then evaporated, the residue extracted with boiling alcohol, as before, the alcohol collected on a watch-glass, previously weighed, and allowed to evaporate. The residue consists of pure cholesterine, the quantity of which may be estimated by weight.

The accuracy of this process may be tested by means of the microscope. As the crystals have so distinctive a form under the microscope, it is easy to determine by examining the watch-glass, whether it has been obtained in a state of purity. In making this analysis quantitatively, it is necessary to be very careful in all the manipulations; and for determining the weight of such minute quantities, an accurate and delicate balance, one, at least, that will turn with the thousandth of a gramme, carefully adjusted, must be employed. With these precautions, the quantity of cholesterine in any fluid or solid may be determined with perfect accuracy. The quantity of cholesterine may be estimated in from fifteen to twenty grains of blood. In analyzing the brain and bile, I found it necessary to pass the first ethereal solution through animal charcoal, to get rid of the colouring matter. In doing this, the charcoal must be washed with fresh ether till the solution which passes through is brought up to the original quantity. The other manipulations are the same as in examinations of the blood. In examining the meconium, I found that the cholesterine which crystallized from the first alcoholic extract was so pure that it was not necessary to subject it to the action of an alkali.

I am aware that in describing the process for the extraction of cholesterine I have entered into details which would be superfluous for the practical chemist. But the extraction of this substance from the blood is so simple, and the results of the examination of blood in different parts of the circulatory system have been so striking and important, that I cannot but indulge the hope that the observations which follow will be verified by those who may not be skilful practical chemists. Almost any one is competent to make a quantitative analysis of the blood for cholesterine. It simply requires six days for the process, and a number of analyses may be carried on at the same time. It requires one day, after the blood has been dried and pulverized, for the ether to act upon it; the next morning it is filtered and set aside; the next morning it will be dry, and may be extracted with alcohol, and set aside to evaporate; the next morning it may be treated with potash, filtered, and the filter washed with water; the following day it may be washed with ether, and set aside to evaporate; the following day it will have evaporated, and may be extracted with hot alcohol; and the following day the alcohol will have evaporated, and the specimen may be examined by the microscope and weighed. All that is required is a little care in the performance of these simple manipulations—which one with a slight acquaintance with operations in chemistry may perform at once, and

one or two trials will enable a novice to execute—and accuracy in weighing, which is, indeed, the most delicate part of the process.

History of cholesterine.—A brief sketch of the history of this substance may not be uninteresting. It was first obtained by Poulletier de la Salle, in 1782, who extracted it from a biliary calculus. He communicated his observations to Fourcroy, who published them, after having verified his experiments, the death of the discoverer preventing him from making his observations public. Afterwards, in examining an old, hardened, liver, Fourcroy found a concrete, oily substance, analogous to that discovered by Poulletier. He imagined that the liver had become changed into a substance resembling spermaceti. The cholesterine was afterwards found in gall-stones, by Vicq d'Azyr, by Jaquin, Titius and Kreysig. In 1791 Fourcroy described a substance which he called adipocire, found in bodies at the *cimetière des Innocents*, which he likened to spermaceti and to cholesterine. He always, however, made a distinction between these substances; calling the cholesterine *crystallizable adipocire.* In 1814 Chevreul established the difference between the adipocire and the cholesterine, giving a full description of the cholesterine. He extracted it from the bile of the human subject, of the bear, and of the pig.

After that time a number of chemists found it in the gall-stones and intestinal concretions. Lassaigne found it in a cerebral tumour, Guérard in hydatid cysts of the liver, Morin in the liquid from an abdominal tumour, Caventou in the matter from an abscess under the malar bone, and a number of others in tumours in various situations. In 1830 it was discovered in the blood by Denis, and afterwards described by Boudet, who wrote an elaborate article on the composition of the serum of the blood in 1833, in which he describes the cholesterine and a new substance which he called *seroline.*[1] It was also detected in normal blood by Lecanu and Marchand. Couerbe, who made elaborate researches into the chemical composition of the cerebral substance, pointed out the existence of cholesterine in the brain. Lebert found it in the substance of cancerous tumours, Curling found it in the fluid of hydrocele, Simon extracted it from the meconium, and Preuss discovered it in the substance of crude tubercle. Of late authors, Becquerel and Rodier have been most extended in their investigation of this principle.[2] They have made a number of careful quantitative analyses of the blood for this substance in health and disease. Their observations will be more particularly referred to further on.[3]

[1] Boudet, Nouvelles Recherches sur la composition du serum du sang humain. Annales de Chimie et de Physique, tom. lii. p. 337.

[2] Traité de Chimie Pathologique appliquée à la médecin pratique, par M. Alf. Becquerel, Professeur agrégé, etc., et par M. A. Rodier, Docteur en Médecine, etc. Paris, 1854, and Recherches sur la composition du sang. Paris, 1844.

[3] The history of the cholesterine was mostly compiled from the excellent work of Robin and Verdeil, the Chimie Anatomique.

Functions of the cholesterine.—By experiments which I have performed upon the lower animals, and by certain facts which have been developed by observations on the human blood in health and disease, I conceive that I have been enabled to solve the problem of the function of cholesterine.

Cholesterine is an excrementitious product, formed in great part by the destructive assimilation of the brain and nerves, separated from the blood by the liver, poured into the upper part of the small intestine with the bile, transformed in its passage down the alimentary canal into ster-corine (the seroline of Boudet, a substance differing very little from cholesterine), *and, as stercorine, discharged by the rectum.*

The quotation with which I prefaced this paper expresses the actual state of the science with regard to cholesterine. Still, though our actual knowledge of its function has been so slight, a few writers on chemical physiology and on physiology, taking the limited data on this subject, make reference to it as an effete substance. With regard to its relation to the brain, some think that it is formed in the brain and taken up by the blood, while others think that it is formed in the blood and deposited in the brain. All the views with regard to its effete properties are, of course, based on the supposition that it is discharged in the feces. Effete matters are discharged from the body, and this would find its exit by the anus, since it has never been detected in the urine. These conjectures have attracted little attention in the scientific world; and these views being based on the supposition that this substance is formed in the fecal matters, fall to the ground from the fact that no one as yet detected it in the feces. The fact that cholesterine is so generally considered an ingredient of the feces may be thus explained. It is poured into the alimentary canal with the bile; no one has shown what becomes of it, the chemistry of the feces being little understood, and therefore it has been assumed that it is found in the feces. That the facts which we have with regard to cholesterine render its effete properties possible, and, perhaps, probable, is certainly true; but these facts are merely sufficient to enable the scientific investigator to address an intelligent inquiry to nature on this subject; they do not resolve the question. In the experiments which form the basis of this article, the inquiry was made and the answer obtained; some others have, without much reflection, apparently, made simple statements which approximate in some degree to the facts. The only way these assertions could be sustained is by the labour which I have expended in eliciting from nature a reply to my interrogatories.

The works which I have had an opportunity of consulting where any decided opinion relative to the function of cholesterine has been expressed, are those of Carpenter, Lehmann, Mialhe, and Dalton.[1]

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[1] These authors are quoted in the order in which their publications appeared.

Carpenter, in the fifth American edition of his Human Physiology, 1853, has the following with regard to the function of cholesterine.

" It is also stated to be a constituent of the nervous tissue, having been extracted from the brain by Couerbe, and other experimenters; but it may be doubted whether this is not rather a product of the disintegration of nerve-substance, which is destined to be taken back into the blood for elimination by the excretory apparatus, like the kreatine which may be extracted from the juice of flesh, or the urea which is obtainable from the vitreous humour of the eye, both being undoubtedly excrementitious matters. For cholesterine is a characteristic component of the biliary excretion, and is closely related to its peculiar acids ; so that it can scarcely be looked upon in any other light than as an excrementitious product, the highest function of which is to assist in the support of the calorifying process. It is frequently separated from the blood as a morbid product; thus it is often present in considerable quantity in dropsical fluids, and particularly in the contents of cysts ; and it may be deposited in the solid form in degenerated structures, tubercular concretions, &c."[1]

In Lehmann, we find the following on this subject :—

" Judging from the mode of its occurrence, we must regard it as a product of decomposition ; but from what substances and by what processes it is formed, it is impossible even to guess. Notwithstanding the similarity which many of its physical properties present to those of the fats, we can hardly suppose that it takes its origin from them, since the fats, for the most part, become oxidized in the animal body, whereas in order to form cholesterine, they must undergo a process of deoxidation."[2]

I translate the following from the excellent work of Mialhe, on Chemistry applied to Physiology and Therapeutics, Paris, 1856, the paragraph entitled " Source of Cholesterine in the Animal Economy."

" We have just examined in what manner the fatty bodies penetrate into the blood. Some eminent *savans* have held that the fatty matters from the exterior are the only ones which exist in the economy, and that it is incapable of producing these in itself. Now it is an opposite opinion which tends to predominate, and the majority of physiologists think that certain fatty bodies take origin in the very substance of our organism. This last mode of origin seems at least incontestable for the cholesterine, which has not yet been found in the vegetable kingdom.

" But what are the chemico-physiological reactions which preside over the development of this particular fatty substance ?

" There are for us two modes for comprehending the formation of the cholesterine at the expense of the elements of the blood. Cholesterine may come from the fatty matters ; it would be, in this case, like the final result or last stage of chemical modifications which the fatty matters undergo in the animal economy.

" This manner of viewing it is slightly probable ; for, in order that it should be true, it would be necessary that the fatty bodies, in oxidizing, should give rise to a compound richer than they in carbon. We know, indeed, that cholesterine is, of all fatty bodies, the one which contains the most carbon.

" We think that we should reject that opinion and stop at the following.

" The production of cholesterine may be attributed to a transformation of the albuminoid materials, a transformation analogous to that which has been pointed out by M. Blondeau de Carrolles in cheese, and which that chemist has designated under the name of adipose fermentation. The large proportion of carbon which the cholesterine contains, and which approximates it to albuminous matters, would come to the support of that point of view. The retardation of the

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[1] Carpenter's Principles of Human Physiology, page 74. Philadelphia, 1853.

[2] Physiological Chemistry, by Professor C. G. Lehmann, vol. i. 248. Philadelphia, 1855.

circulation, and the deficiency of oxidation which is the consequence of it, explains also why the cholesterine is in much greater proportion in the closed cavities than in the blood itself.

" Whichever it may be of these two opinions, it is incontestable for us that, if the cholesterine be not burned with the other matters proper to respiratory alimentation, it is solely on account of its chemical inertia; cholesterine, indeed, is to fatty matters what mannite is to saccharine substances—what urea is to albuminoid matters; that is to say, that it constitutes a kind of *caput mortuum*, of which the organism has only to free itself. It is certain also, for us, that if the cholesterine is not found in all the excrementitious liquids, where most of the other products existing in the blood are found, it is solely on account of its insolubility.

" The preceding remarks explain perfectly, to our eyes at least, why the pre- sence of cholesterine has never been established in the urine of man, either in the form of crystals, or ' calculi,' while this substance is found in the bile, where it very often forms calculi of considerable size. Cholesterine, indeed, is insoluble in acid liquids, such as the urine; while it is soluble in soapy liquids, such as the bile. Such is solely the reason why the cholesterine is excreted by the biliary passages."[1]

Finally, in Dalton's *Treatise on Human Physiology,* we find the fol- lowing paragraph in which the subject of cholesterine is considered :—

" CHOLESTERINE ($C_{25}H_{22}O$).—This is a crystallizable substance which resem- bles the fats in many respects, since it is destitute of nitrogen, readily inflam- mable, soluble in alcohol and ether, and entirely insoluble in water. It is not saponifiable, however, by contact with the alkalies, and is distinguished on this account from the ordinary fatty substances. It occurs, in a crystalline form, mixed with colouring matter, as an abundant ingredient in most biliary calculi, and is found also in different regions of the body, forming a part of various morbid deposits. We have met with it in the fluid of hydrocele, and in the in- terior of many encysted tumours. The crystals of cholesterine have the form of very thin, colourless, transparent, rhomboidal plates, portions of which are often cut out by lines of cleavage parallel to the sides of the crystal. They frequently occur deposited in layers, in which the outlines of the subjacent crystals show very distinctly through the substance of those which are placed above. Choles- terine is not formed in the liver, but originates in the substance of the brain and nervous tissue, from which it may be extracted in large quantity by the action of alcohol. From these tissues it is absorbed by the blood, then conveyed to the liver, and discharged with the bile."[2]

The above extracts embrace all that I have been able to find bearing on the question of the function of cholesterine. The extracts from Mialhe and Dalton contain all that is said by them on this subject. Those from Carpen- ter and Lehmann contain only what bears on the function of this substance, the chemical details being omitted. Of the authors cited, Mialhe is the most extended on the subject, and is almost the only one who adduces any arguments to support his views; but his opinions are biased by the purely chemical view which he takes of the subject, and are involved with the ideas with reference to plastic and calorific food, now rejected by many

[1] Chimie appliquée à la Physiologie et à la Thérapeutique. Par M. le Docteur Mialhe. Page 191. Paris, 1856.

[2] A Treatise on Human Physiology, designed for the use of Students and Prac- titioners of Medicine. By John C. Dalton, Jr., M. D., Professor of Physiology and Microscopic Anatomy in the College of Physicians and Surgeons, New York, &c. Page 189. Philadelphia, 1861.

eminent physiologists, and which, I conceive, will be so little supported by future advances in science, that they will soon be universally discarded, in the exclusive sense in which they are received by him. Putting these hypotheses aside, we examine the actual state of our science, with regard to cholesterine, and we find that the function, up to this time, has not been established. We will now proceed to the facts which tend to support the statement I have made on this point.

Cholesterine exists in the blood, from which it may be extracted in a state of purity, and estimated by the process which I have already indicated. Becquerel and Rodier have made analyses of the healthy human blood for this substance with the following results:—

Venous blood of the male .   .   .   .   0.09 pts. per 1.000
" " " female .   .   .   0.09 "   "   "

I have made a quantitative analysis of three specimens of healthy human blood with the following results :—

	Quantity of Blood. grains.	Cholesterine. grains.	Proportion per 1,000 pts.
Venous blood from the arm; male æt. 35	312.083	0.139	0.445
Do. do. do. (coloured) æt. 22	187.843	0.123	0.658
Do. do. do. æt. 24	102.680	0.077	0.751

These three analyses were all carried on at the same time, and each specimen subjected to precisely the same process. The results show a wide range within the limits of health. The difference was not due to any variation relating to the digestive process, as the specimens were all drawn at the same time, and were taken from prisoners on Blackwell's Island, who were subjected to the same diet, and ate at the same time. It will be seen by this table that I have obtained from five to eight times as much as is indicated by Becquerel and Rodier. I can only explain this by the fact that I operated on the whole blood, while they only analyzed the serum. Boudet states that it is necessary to make three to four copious bleedings, and mix the serum in order to obtain a sufficient quantity for a satisfactory analysis. I have operated on about fifty grains of blood with success, and have no doubt but that I would be able to extract the cholesterine in a crystalline form, and estimate its quantity in fifteen and twenty grains. The purity of the extract can easily be demonstrated by a microscopic examination. I conclude, then, that a much larger quantity of cholesterine exists normally in the blood than has been supposed, and that its variations, in different persons, within the limits of health, are considerable.

The next question which naturally arises is the origin of the cholesterine. When we examine the situations in which it is found, we find that it exists in largest quantity in the substance of the brain and nerves. It is also found in the substance of the liver, probably in the bile which is contained in this organ, and the crystalline lens, but with these exceptions it is found

only in the nervous system and blood. Two views present themselves with regard to its origin. Cholesterine is deposited in the nervous matter from the blood, or is formed in the brain and taken up by the blood. This is a question, however, which can be settled experimentally, by analyzing the blood for cholesterine as it goes to the brain by the carotid, and as it comes from the brain by the internal jugular. The cholesterine being found also in the nerves, and, of course, a large quantity of nervous matter existing in the extremities, it is desirable at the same time to make an analysis of the venous blood from the general system.

With reference to this question the following experiment was made:—

Exp. 3. A medium sized dog, about six months old, fasting, was put under the influence of ether. The carotid and internal jugular were exposed on the left side, and the animal allowed to come out from the effects of the anæsthetic. Two hours after, he was again etherized, and the blood taken from the following vessels in the order in which they are named : 1, Internal jugular ; 2, Carotid ; 3, Vena cava ; 4, Hepatic veins ; 5, Hepatic artery ; 6, Portal vein. In the operation of drawing the blood from the abdominal vessels, immediately after opening the abdomen a ligature was applied to the vena cava and a little blood taken, which prevented the blood from the inferior extremities from mixing with the hepatic blood. The blood was then taken from the hepatic veins, a matter of some difficulty, as it is always more or less mingled with blood returning through the thoracic vena cava, and a ligature applied to the hepatic artery and portal vein. The blood was then drawn from the hepatic artery and portal vein.[1] A quantity of bile was then taken from the gall-bladder, and a portion taken from the substance of the brain. These specimens were received into carefully weighed vessels and weighed ; but as I failed to make a quantitative analysis, my process of extraction not having been perfected, it is unnecessary to enter into their details. They were then dried and pulverized, treated with ether, evaporated, the residue extracted with hot alcohol, allowed to evaporate spontaneously, and examined with magnifying powers of 70, 270, and 400 diameters successively. The residue of the bile and brain were found to consist of nearly pure cholesterine, but in all the other specimens, excepting that from the internal jugular, the appearance of cholesterine was doubtful. They all contained, with masses

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[1] The operation of collecting the blood from any particular vessel is by no means so easy as might at first be supposed. The greatest care is necessary in order to obtain it unmixed. This is particularly so in the case of the hepatic vein, the unmixed blood from which it is exceedingly difficult to obtain. In drawing blood, the operation must be done as rapidly as possible to avoid the derangements of the circulation which arise from exposure of the vessels, pressure, etc. In taking blood going to and coming from a part, it must always be taken from the vein first ; as ligating or compressing the artery would of course arrest the circulation. As the blood in the arterial system is not subject to the same changes in composition as the blood in the different veins, any specimen of the arterial blood will represent the blood going to a part, unless, like the liver, it receives blood from the venous system. The collection of blood I have found the most difficult part of these investigations.

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of ordinary fat, crystals of stercorine.[1] There were a few distinct plates of cholesterine in the specimen from the internal jugular. The specimens were then treated with a solution of caustic potash and set aside. In two days part of the potash was removed with bibulous paper and portions of the precipitates taken out, placed upon slides, and examined microscopically with $\frac{1}{6}$th and $\frac{1}{12}$th inch objectives successively. The watch-glasses were then set aside, carefully protected from the dust, and examined again ten days after, when they had become entirely dry. The following was the result of the examinations of the extracts of blood from the carotid, internal jugular, vena cava, and the extract of the brain. The examination of the other specimens has nothing to do with the question now under consideration, and their description is deferred.

Blood from the carotid artery.—First examination, three days after the operation, discovered a large number of small crystals of stercorine and masses of fat; but after the most careful examination, prolonged for two hours, I failed to discover any crystals of cholesterine. The appearance is represented in Fig. 2.

The second examination, eleven days after, discovered a small quantity of cholesterine mixed with the matters noted in the first examination. This appearance is represented in Fig. 3.

Substance of the brain.—All the microscopic examinations of the extract from the brain showed crystals of cholesterine in large quantity. The crystals from the brain are described by Robin as being thinner and more elongated than those found in other situations.[2] This peculiarity I also noticed. The appearance is represented in Fig. 4.

Blood from the internal jugular.—In the first examination of the specimen from the internal jugular, after the blood had been treated with ether, the ether allowed to evaporate, and the residue extracted with hot alcohol, well-marked plates of cholesterine were noted. At this time it could not be discovered in any of the other specimens of blood after the most careful and patient examination. After the caustic potash had been added, the cholesterine was demonstrated in large quantity, with a few crystals of stercorine. The appearance is represented in Fig. 5, which was drawn eleven days after the blood was collected. Another examination was made on the following day, which showed, in addition to the cholesterine, a considerable quantity of stercorine. (See Fig. 6.)

Blood from the vena cava.—The extract of the blood from the vena cava, examined eleven days after the blood was drawn, showed a large quantity of stercorine and a few crystals of cholesterine. The cholesterine was distinct but not very abundant. (See Fig. 7.)

These experiments, the first that I made on this subject, demonstrate the following facts : 1. That the brain contains a large quantity of choles-

[1] Stercorine, or seroline, is a non-saponifiable fatty substance resembling the cholesterine in many of its chemical properties, but fusing at a much lower temperature. It was discovered in the serum of the blood by Bou̧det about 1833. It crystallizes in the form of needles, which will be more particularly described when we treat of the extraction of this substance from the feces. As I have found it in great abundance in the feces, and am disposed to doubt its existence as a natural constituent of the serum of the blood, I have called it *stercorine*, for reasons which will be more fully exposed further on.

[2] Traité de Chimie Anatomique, Robin and Verdeil, tome iii. p. 57.

terine (which had, however, been previously established). 2. That the blood going to the brain contains a small quantity of cholesterine, while the blood coming from the brain contains a large quantity. 3. That the blood coming from the lower extremities and pelvic organs contains more choles-terine than the blood carried to them by the arterial system.

It was only necessary to confirm these statements by further investiga-tion, to be enabled to deduce from them the following important conclu-sion : *i. e.* That cholesterine is formed in some of the tissues of the body; and, judging from the fact that the nervous tissue is the only one in which it is found, and that the blood gains it in its passage through the great nervous centre, it is formed, in great part, by the nervous system. After the first experiment, which almost confirmed the supposition with which I had started, I directed my attention to the perfection of a process by which I might make an accurate quantitative analysis of the blood for cholesterine, so as to be able to state positively that it gained cholesterine in its pas-sage through certain organs, and furthermore to determine the amount of increase. After a number of experiments, I fixed upon the process which I have minutely described in the first part of this article, and made the following experiments for the purpose of ascertaining the quantity of cholesterine produced in the brain.

Exp. 4. A medium sized adult dog was put under the influence of ether and the carotid artery, internal jugular, and femoral veins exposed. Spe-cimens of blood were drawn, first from the internal jugular, next from the carotid, and last, from the femoral vein. These specimens were received into carefully weighed vessels, and weighed.

They were then analyzed for cholesterine by the process described on pages 313–315, and the following results obtained :—

	Quantity of Blood. grains.	Cholesterine. grains.	Cholesterine per 1,000 pts.
Carotid	179.462	0.139	0.774
Internal jugular . .	134.780	0.108	0.801
Femoral vein . . .	133.886	0.108	0.806

Percentage of increase in blood from the jugular over the arterial blood 3.488
Do.   do.   of blood from femoral vein 4.134

This experiment shows an increase in the quantity of cholesterine in the blood during its passage through the brain and an increase, even a little greater, in the blood passing through the vessels of the posterior extremity. To facilitate the operation, however, the animal was brought completely under the influence of ether, which, from its action on the brain, would not improbably produce some temporary disturbance in the nutrition of that organ, and consequently interfere with the experiment. For the purpose of avoiding this difficulty I performed the following experiments without administering an anæsthetic.

Exp. 5. A small young dog was secured to the operating table, and the internal jugular and carotid exposed on the right side. Blood was taken, first from the jugular, and afterwards from the carotid. The femoral vein

on the same side was then exposed and a specimen of blood taken from that vessel. The animal was very quiet under the operation, though no anæsthetic was used, so that the blood was drawn without any difficulty and without the slightest admixture.

The three specimens were analyzed for cholesterine with the following results :—

	Quantity of Blood. grains.	Cholesterine. grains.	Cholesterine per 1,000 pts.
Carotid	143.625	0.679	0.967
Internal jugular	29.956	0.046	1.545
Femoral vein	45.035	0.046	1.028

Percentage of increase in blood from the jugular over arterial blood   59.772

Do.   do.   of blood from the femoral vein   .   .   .   6.308

Exp. 6. A large and powerful dog was secured to the operating table and the carotid and internal jugular exposed. Specimens of blood were taken from these vessels, first from the jugular, carefully weighed and analyzed for cholesterine in the usual way. The following results were obtained :—

	Blood. grains.	Cholesterine. grains.	Proportion in 1,000 pts.
Carotid	140.847	0.108	0.768
Internal jugular	97.811	0.092	0.947

Percentage of increase in passing through the brain   .   .   .   23.307

Exp. 5 shows a very considerable increase in the quantity of cholesterine in the blood passing through the brain, while it is comparatively slight in the blood of the femoral vein. The proportion of cholesterine is also large in the arterial blood compared with other observations.

Exp. 6 shows but a slight difference in the quantity of cholesterine in the arterial blood in the two animals; the proportion in the animal that was etherized being 0.774 pts. per 1,000, and in the animal that was not etherized 0.768 per 1,000, the difference being but 0.006; but, as I had suspected, the ether had an influence on the quantity of cholesterine absorbed by the blood in its passage through the brain. In the first instance the increase was but 3.488 per cent., while in the latter it was 23.307. Unfortunately the blood was not taken from the femoral vein. I intended to take blood from the abdominal organs, but after opening the abdomen the struggles of the animal were so violent that this was impossible, and he was killed.

What are our natural conclusions, from the preceding experiments, with regard to the origin of cholesterine in the economy? It has been found that the brain and nerves contain a large quantity of this substance, which is found in none other of the tissues of the body. The preceding experiments, especially Exps. 5 and 6, show that the blood which comes from the brain contains a much larger quantity of cholesterine than the blood which goes to this organ.

The conclusion is, then, that it is produced in the brain, and thence absorbed by the blood.

But the brain is not the only part where cholesterine is produced. It

will be seen by Exp. 4 that there is 4.134 per cent., and in Exp. 5, 6.308 per cent. of increase in the cholesterine in the passage of the blood through the inferior extremities, and probably about the same in other parts of the muscular system. In examining these tissues chemically, we find that the muscles contain no cholesterine, but that it is abundant in the nerves; and as we have found that the proportion of cholesterine is immensely increased in the passage of the blood through the great centre of the nervous system, taken, as the specimens examined were, from the internal jugular, which collects the blood from the brain and very little from the muscular system, it is rendered almost certain, that in the general venous system, the choles-terine which the blood contains is produced in the substance of the nerves.

If this be true, and if, as I hope to show, the cholesterine be a product of the destructive assimilation of nervous tissue, its production would be proportionate to the activity of the nutrition of the nerves; and anything which interfered to any great extent with their nutrition would diminish the quantity of cholesterine produced. In the production of urea by the general system, which is an analogous process, muscular activity increases the quantity, and inaction diminishes it, on account of the effect upon nutrition. In cases of paralysis we have a diminution of the nutritive forces in the parts affected, especially of the nervous system, which, after a time, becomes so disorganized, that although the cause of the paralysis be removed, the nerves cannot resume their functions. It is true we have this to a certain extent in the muscles; but it is by no means as marked as it is in the nerves. We should be able then to confirm the observations on animals, by examining the blood in cases of paralysis; when we should find a very marked difference in the quantity of cholesterine, between the venous blood coming from the paralyzed parts, and that from other parts of the body. With this in view I made analyses of the blood from both arms in three cases of hemiplegia, which seemed to me most suitable for such a comparison.

CASE I. Sarah Rumsby, æt. 47, affected with hemiplegia of the left side. Two years ago she was taken with apoplexy, and was insensible for three days. When she recovered consciousness she found herself paralyzed on the left side. Said she had epilepsy four or five years before the attack of apoplexy. Now she has entire paralysis of motion on the affected side, with the exception of some slight power over the fingers, but sensation is perfect. The speech is not affected. The general health is good.

CASE II. Anna Wilson, æt. 23, Irish, affected with hemiplegia of the right side. Four months ago she was taken with apoplexy, from which she recovered in one day with loss of motion and sensation on the right side. She is now improving and can use the right arm slightly. The leg is not so much improved, because she will make no effort to use it.

CASE III. Honora Sullivan, Irish, æt. 40, affected with hemiplegia of right side. About six months ago she was taken with apoplexy, and recovered consciousness the next day, with paralysis. The leg was less affected than the arm, from the first. The cause was supposed by Dr. Flint,

the attending physician, to be due to an embolus. Her condition is now about the same as regards the arm, but the leg has somewhat improved.

These cases all occurred at the Blackwell's Island Hospital. The treatment in all consisted of good diet, frictions, passive motion, and use of the paralyzed members as much as possible.

A small quantity of blood was drawn from both arms in these three cases. It was drawn from the paralyzed side, in each instance, with great difficulty, and but a small quantity could be obtained.

The specimens were all examined for cholesterine with the following results :—

Table of Quantity of Cholesterine in Blood of Paralyzed and Sound Sides in three cases of Hemiplegia.

	Blood.	Choles-terine.	Cholesterine per 1,000.
	grains.	*grains.*	
Case I. Paralyzed side.	55.458	—	The watch-glass contained 0.031 grain of a substance, but the most careful examination failed to show a single crystal of cholesterine.
Do. Sound side.	128.407	0.062	0.481.
Case II. Paralyzed side.	18.381	—	Same as Case I.
Do. Sound side.	66.396	0.062	0.808.
Case III. Paralyzed side.	21.842	—	Same as Case I.
Do. Sound side.	52.261	0.031	0.579.

The result of these examinations is very interesting: not a single crystal of cholesterine was found in any of the three specimens of blood from the paralyzed side, while about the normal quantity was found in the blood from the sound side. As the nutrition of other tissues is interfered with in paralysis, it is impossible to say positively from these observations alone, that the cholesterine is produced in the nervous system only. But the nutrition of the nerves is undoubtedly most affected; and this observation, taken in connection with the preceding experiments on animals, seem to settle where the cholesterine is produced.

We may extend our first conclusion, then, and state that the *cholesterine is produced in the substance of the nervous system.*

Before entering upon the character of cholesterine, and inquiring whether it be an excrementitious or a recrementitious product, we will endeavour to follow it out in the system and ascertain if there be any organ which separates it from the blood. In pursuing this question, the method will be adopted that has been employed in investigating its origin; that is, analyzing the blood as it goes to and comes from certain organs. The organ which we would be led first to examine is the liver, as it is the only gland, the product of which contains cholesterine, which, if not manufactured in the gland itself, must be separated from the blood.

In the first series of experiments which I performed on this subject, I endeavoured to show on the same animal the origin of cholesterine in certain parts, and its removal from the body. In these experiments, which were only approximative, as I had not then succeeded in extracting the cholesterine perfectly pure, I commenced with the arterial blood, examining it as it went into the brain by the carotid, analyzing the substance of the brain, then analyzing the blood as it came out of the brain by the internal jugular, examining the blood as it went into the liver by the hepatic artery and portal vein, examining the secretion of the liver, then the blood as it came out of the liver by the hepatic vein, examining also the blood of the vena cava in the abdomen. The analyses of the blood from the carotid, internal jugular, and vena cava have already been referred to, pages 323, 324, in treating of the origin of the cholesterine. It will be remembered that there was a large quantity of this substance in the internal jugular, and but a small quantity in the carotid, showing that it was *formed* in the brain. I now give the conclusion of those observations, which bears upon the *separation* of the cholesterine from the blood.

Exp. 7. Specimens of blood were taken from the hepatic artery, portal vein and hepatic vein, and a small quantity of bile from the gall-bladder. These specimens were treated in the manner already indicated in Exp. 3; *i. e.*, evaporated and pulverized, extracted with ether, the ether evaporated, and the residue extracted with boiling alcohol, this evaporated, a solution of caustic potash added and then subjected to a microscopic examination.

Blood from the portal vein.—Microscopic examination of the extract from the portal vein showed quite a number of crystals of cholesterine, which are represented in Fig. 8. These were observed after the fluid had nearly evaporated.

Blood from the hepatic artery.—Microscopic examination of the extract from the hepatic artery, made after the fluid had nearly evaporated, showed a considerable amount of cholesterine; more than was observed in the preceding specimen. (See Fig. 9.) There were also observed a few crystals of stercorine, represented in Fig. 10.

Blood from the hepatic vein.—The first examination of the extract from the hepatic vein, which was made just before the potash was added, showed a number of fatty masses with some crystals of stercorine. The solution of potash was then added, and two days after, another careful examination was made, discovering nothing but fatty globules and granules. (See Fig. 11.) The watch-glass was then set aside, and was examined eleven days after, when the fluid had entirely evaporated. At this examination, a few crystals of cholesterine were observed for the first time. (See Fig. 12.) There were also a number of crystals of margaric and stearic acid.

Bile.—All the examinations of the extract from the bile showed cholesterine; the precipitate consisted, indeed, of this substance in a nearly pure state. Fig. 13 represents some of the crystals which were observed in this specimen.

This series of experiments being taken in connection with the first observations on the carotid and internal jugular, while the one series demonstrates pretty conclusively that cholesterine is formed in the brain, the other shows

that it disappears, in a measure, from the blood in its passage through the liver, and is found in the bile. In other words, it is formed in the nervous tissue, and prevented from accumulation in the blood by its excretion by the liver. This suggests an interesting series of inquiries; and this fact, substantiated, would be as important to the pathologist as to the physiologist. But in order to settle this important question, it is necessary to do something more than make an approximative estimate of the quantity of cholesterine removed from the blood by the liver. The quantity which is thus removed in the passage of the blood through this organ should be estimated, if possible, as closely as the quantity which the blood gains in its passage through the brain. But this estimate is more difficult. The operation for obtaining the blood, in the first place, is much more serious than that for obtaining blood from the carotid and internal jugular. It is very difficult to obtain the unmixed blood from the hepatic vein ; and the exposure of the liver, if prolonged, must interfere with its eliminative function, in the same way that exposure of the kidneys arrests, in a few moments, the flow from the ureter. It is probable, however, that the administration of ether does not interfere with the elimination of cholesterine by the liver as it does, apparently, with its formation in the brain. Anæsthetics, we know, have a peculiar and special action on the brain, but do not interfere with the functions of vegetative life, like secretion or excretion ; and, we would suppose, would not interfere with the depurative function of the liver. It is fortunate that this is the case, for the operation of taking blood from the abdominal vessels is immensely increased in difficulty by the struggles of an animal not under the influence of an anæsthetic, so much so, indeed, that I failed entirely in obtaining any blood from one animal (the one used in Exp. 6), which was not etherized. It was a very powerful dog, and his struggles were so violent that it was impossible to collect the blood accurately from the abdominal vessels, and the attempt was abandoned. With the view of settling the question of the disappearance of a portion of the cholesterine of the blood in its passage through the liver, by an accurate quantitative analysis, I repeated the operation for drawing blood from the vessels which go into, and emerge from the liver. In my first trial the blood was drawn so unsatisfactorily, and the operation was so prolonged, that I did not think it worth while to complete the analysis, and abandoned the experiment. In the following one I was more successful.

Exp. 8. A good-sized bitch (pregnant) was brought completely under the influence of ether, the abdomen laid freely open, and blood drawn, first from the hepatic vein, and next from the portal vein. The taking of the blood was entirely satisfactory, the operation being done rapidly, and the blood collected without any admixture. A specimen of blood was then taken from the carotid to represent the blood from the hepatic artery.

The three specimens of blood were then examined in the usual way for cholesterine, with the following results :—

	Blood. grains.	Cholesterine. grains.	Cholesterine in 1000 pts.
Arterial blood . . .	159.537	0.200	1.257
Portal vein . . .	168.257	0.170	1.009
Hepatic vein . . .	79.848	0.077	0.964

Percentage of loss in arterial blood in its passage through the liver   23.309
    Do.   do.   do. of portal vein 4.460

This experiment proves positively that there was good ground for sup-posing from Exp. 7, namely, that cholesterine is separated from the blood by the liver; and here we may note, in passing, a striking coincidence between the analysis in Exp. 6, when the blood was studied in its pas-sage through the brain, and the one just mentioned, when the blood was studied in its passage through the liver. *The gain of the arterial blood in cholesterine in passing through the brain was 23.307 per cent., and the loss of this substance in passing through the liver is 23.309 per cent.* There must be, of course, the same quantity separated by the liver that was formed by the nervous system, it being formed, indeed, only to be sepa-rated by this organ, its formation being continuous, and its removal neces-sarily the same, in order to prevent its accumulation in the circulating fluid. The almost exact coincidence between these two quantities, in specimens taken from different animals, though not at all necessary to prove the fact just mentioned, is still very striking.

It is shown by Exp. 8 that the portal blood, as it goes into the liver, contains but a small percentage of cholesterine over the blood of the hepatic vein, while the percentage in the arterial blood is large. The arte-rial blood is the mixed blood of the entire system, and as it probably passes through no organ before it gets to the liver which diminishes its choleste-rine, contains a quantity of this substance, which must be removed. The portal blood, coming from a limited part of the system, contains less of this substance, though it gives up a certain quantity. In the circulation of the liver, the portal system largely predominates, and is necessary to other im-portant functions of this organ, such as the production of sugar and fat. Soon after the portal vein enters the liver, its blood becomes mixed with that from the hepatic artery,[1] and from this mixture the cholesterine is separated. It is only necessary that blood, containing a certain quantity of cholesterine, should come in contact with the bile-secreting cells, in order that this substance be separated. The fact that it is eliminated by the liver is proven with much less difficulty than that it is formed in the nervous system. In fact, its presence in the bile, the necessity of its constant re-

[1] According to Robin, the branches of the hepatic artery are distributed almost entirely in the interlobular plexuses, and on the walls of the hepatic duct and portal vein, and do not find their way into the substance of the lobules.—*Diction-naire de Médecine, de Chirurgie, de Pharmacie, des Sciences accessoires et de l'Art vétérinaire de* P. H. Nysten; *onzième édition revue et corrigé.* Par E. Littré et Ch. Robin. Paris, 1858. Article *Foie.*

moval from the blood, which is consequent on its constant formation and absorption by this fluid, are almost sufficient in themselves to warrant the conclusion that it is removed by the liver. This, however, is put beyond a doubt by the preceding analysis of the blood going to and coming from this organ.

Another link, then, is added to the chain of facts which make up the history of cholesterine. The first is that—

Cholesterine is formed in the brain and nervous system, and absorbed by the blood.

The second, which has just been proven, is that—

Cholesterine, formed in these situations, and absorbed by the blood, is separated from the blood in its passage through the liver.

The next question, in following out this line of inquiry, is, What becomes of the cholesterine which is separated from the blood ? This question is very easily answered, and necessitates only an examination of one of the products of the liver, the bile.

The Bile.—In the few remarks with which I prefaced this article, I spoke of the various opinions which are held among physiologists with reference to the function of the bile—some regarding it as purely excrementitious, others placing it among the recrementitious fluids. I detailed experiments which led me to think that it had two distinct functions : one, which is recrementitious, and is probably concerned in digestion to an important degree, but which it is not designed to take up in this connection ; the other, which is excrementitious, and which is necessarily taken up in our discussion of the important principle which we are now considering. A glance at the composition of the bile will show that it is an exceedingly complex fluid ; and physiological investigations into the destination of certain of its ingredients, by Bidder and Schmidt, Dalton and others, have shown that they are not discharged from the body, but resorbed by the blood; though the failure to detect them in the portal blood by the appropriate tests, shows that in this resorption they probably undergo some alteration.[1]   These substances, which have heretofore been considered the most important ingredients of the bile, though their function is obscure, are the glyco-cholate and tauro-cholate of soda, discovered by Strecker in the bile of the ox in 1848.   The following is the composition of the bile given in Dalton's Physiology, which is "based on the calculations of Berzelius, Frerichs, and Lehmann."[2]

[1] For a very complete account of the bile, with original investigations into the destination of the biliary salts, the reader is referred to an article published by Prof. John C. Dalton, Jr., in the American Journal of the Medical Sciences, October, 1857, and the chapter on bile in Dalton's Physiology.

[2] Dalton's Physiology, second edition, page 158.

Composition of Ox Bile.

Water	888.00
Glyco-cholate of soda . . . .⎫	
Tauro-cholate of soda . . . .⎭	90.00
Biliverdine . . . .⎫	
Fats . . . .⎪	
Oleates, margarates, and stearates of soda and potassa .⎬	13.42
Cholesterine . . . .⎭	
Chloride of sodium . . . .⎫	
Phosphate of soda . . . .⎪	
Phosphate of lime . . . .⎬	15.24
Phosphate of magnesia . . . .⎪	
Carbonates of soda and potassa . . . . . .⎭	
Mucus of the gall-bladder	1.34
	1000.00

Of the above ingredients of the bile, we have the biliverdine, which is simply a colouring matter, the fats, with the oleates, margarates, and stearates, which, with the biliary salts, are said to hold the cholesterine in solution, the chloride of sodium, present in all the animal fluids, the phosphates and carbonates, which are simply excreted, and are also ingredients of the urine, leaving, as the most important constituents, of which the function is least understood, the biliary salts and the cholesterine. The biliary salts are probably recrementitious; but the cholesterine is one of the great products of the waste of the system. The bile, then, presents the combined character, so far as its chemical composition is concerned, of a secretion and of an excretion. Let us now contrast these two properties, and see what this fluid has in common with the secretions, and how it obeys the laws which regulate the excretions. In doing this we will first contrast some of the important distinctions between these two classes of products.

Secretions are characterized by certain elements which are manufactured in the substance of the gland, and are found in no other situation. Such is the pancreatine for the pancreatic juice, the pepsin for the gastric juice, the ptyaline for the saliva, and, we may add, the glyco-cholate and tauro-cholate of soda for the bile.

These substances first make their appearance in the substance of the gland itself; they do not pre-exist in the blood; they are discharged from the gland for a special purpose, and when there is no necessity for their action, the discharge does not take place. Illustrations of this are to be found in the digestive fluids, which are true secretions; only poured out when this function is called into action by the ingestion of food, and not discharged from the body, but their elements taken up again by the blood when their function is accomplished. Thus the gastric or pancreatic fluids are never secreted until food is taken into the alimentary canal, and are resorbed with the digested matters.

The flow of the secretions is intermittent, and the gland, during the period of repose, manufactures the elements of the secretion, which are washed out at the duct when the appropriate stimulus (of food, for example) causes a determination of blood to the organ. The gland manufactures the elements of the secretion, and the blood furnishes the menstruum, the water, by means of which they are dissolved and emptied into the duct. If we expose the pancreas of an animal during the intervals of digestion, it is pale and bloodless ; no fluid flows from the duct; but the elements of the pancreatic juice are, nevertheless, in the gland, for if we macerate it in water, we may dissolve them out, and make an artificial pancreatic juice which will have all the reactions and digestive properties of the natural secretion. But if we expose the pancreas of an animal during digestion, the gland is turgid with blood ; the secretion flows from the duct, and the products of the gland are being washed out by the blood—a process which we imitated when we dissolved them out by maceration in water. The late brilliant experiments of Bernard have shown that the function of the glands is regulated by the nervous system, and that the galvanization of certain nerves, by which the nervous force is imitated, will cause a determination of blood to the organ, and induce secretion, while the galvanization of other nerves will contract the vessels, and arrest secretion.

The substances which characterize the secretions, as they are manufactured in the glands and do not pre-exist in the blood, do not accumulate in the blood when the gland is removed, or its functions are interfered with.

The distinctive characters of the secretions, in fact, may be summed up thus :—

Their elements first appear in the glands, and do not pre-exist in the blood. They are not discharged from the body (with the exception of the milk, which is destined for the nourishment of the child). Their flow is intermittent. They are destined to assist in some of the nutritive functions of the body.

Excretions, of which the urine may be taken as a type, have entirely different characteristics.

Excrementitious substances do not first make their appearance in the organs which separate them, but are produced in the general system.

They pre-exist in the blood, having been absorbed by this fluid from the parts of the system in which they are formed, are carried to particular organs, and separated from the blood for the sole purpose of being expelled from the body. An illustration of this is to be found in the urea, which has been detected in the blood and urine, and some of the tissues of the body. This substance, one of the most important excrementitious products, is absorbed by the blood from certain parts of the system, carried to the kidneys, there separated from the blood, and discharged from the body. Though the gastric and pancreatic fluids, and all the secretions proper, are

resorbed with the food after they have acted upon it, the urea may remain any length of time in the bladder, but it is never absorbed.

The flow of the excretions is constant. No period of repose is necessary for the gland to manufacture their elements, as they all pre-exist in the blood. Nutrition is constant, and destructive assimilation, or waste, which necessitates nutrition or repair, is likewise constant. The blood supplies all the wants of the system, and receives all the products of its decay. As the blood is continually being impoverished, it must be regenerated from without; and this is done by food, which is prepared for absorption by digestion. The secreted fluids are mostly concerned in digestion, and as this is an occasional process, the secretions are intermittent. But waste is continually going on, and excrementitious substances are continually forming; and while the necessity for the secretions is occasional, the necessity for the excretions is constant. Though the actual discharge of the latter from the body is occasional, they are constantly being separated from the blood, and accumulate in receptacles, whence they are discharged at appropriate intervals. No such receptacles exist for the secretions proper, except in the instance of the milk, which accumulates in the ducts of the mammary gland, and is the only secretion which is discharged from the body.

If the secreting glands take on an excretory function, as is an occasional pathological occurrence, their flow becomes continuous. We have an example of this in the occasional separation of the urea from the blood by the gastric tubuli. When the kidneys become so affected by disease as to be unable to separate the urea from the system, the accumulation of this excrement in the blood frequently induces other organs to attempt its removal. The gastric tubuli take on that function, and produce a fluid which contains urea. The gastric juice, if we may now so term it, is no longer a secretion, but an excretion, and we find that its flow is no longer intermittent and dependent upon the stimulus of food introduced into the stomach, but is constant, and continues until the irritation caused by the decomposing urea in the stomach induces an inflammation which prevents further secretion. Thus we have an example of an intermittent *secretion*, characterized by a substance manufactured in the gland and not pre-existing in the blood, changed into a constant *excretion*, characterized by a substance which is not manufactured in the gland but pre-exists in the blood.

The substances which characterize the excretions accumulate in the blood when the organ which eliminates them is removed, or its functions are interfered with. It is to this fact that we owed our knowledge that urea pre-existed in the blood. It was detected in that fluid when it had accumulated in animals from which the kidneys had been removed, and in cases of Bright's disease of the kidneys, before our chemical processes were sufficiently delicate to detect it in healthy blood, when the quantity is kept down to a very low standard by its constant elimination by the kidneys.

The characters of the excretions, then, are entirely opposite to those of the secretions.

Their elements pre-exist in the blood, and are not manufactured in the substance of the organs which eliminate them. Their flow is constant. They are separated from the blood merely to be discharged from the body, and are not destined to assist in any of the nutritive functions of the body.

Having thus contrasted the secretions and the excretions, let us examine the bile and note what are the characters which it has in common with either or both of these products.

The bile is characterized by two kinds of principles. One of them, the glyco-cholate and tauro-cholate of soda, *manufactured* in the liver, found in no other fluid than the bile, does not pre-exist in the blood, and associates the bile with the secretions. The other, the cholesterine, pre-exists in the blood and is simply *separated* from it by the liver, giving the bile one of the characters of an excretion.

The biliary salts (the glyco-cholate and tauro-cholate of soda)˜are discharged into the intestinal canal for a special purpose; and this discharge takes place at the beginning of the digestive act. If we expose the liver and gall-bladder of a dog which has not taken food, we will find the gall-bladder distended with bile; but if we examine these organs when digestion is going on, the gall-bladder will be found nearly empty. It is true that after prolonged fasting the bile is discharged into the alimentary canal, but it must be remembered that it contains another ingredient, the cholesterine, which must be discharged from the body, as we will see presently. The biliary salts are not discharged from the body. Dr. Dalton has shown that the substances extracted from the contents of the large intestine by evaporation, extraction of the residue with alcohol and precipitation with ether, will not react with Pettenkoffer's test, which is a very delicate test for the biliary salts. I have treated the feces of the human subject in the same way with the same result. These salts, therefore, are not discharged from the body unchanged. The next question to determine is whether they are discharged from the body in a modified form. They contain a certain amount of sulphur, of which, as has been shown by Bidder and Schmidt, only one-fifteenth part of the entire quantity which enters the intestine with the bile can be detected in the feces. As sulphur is an elementary substance, it cannot be decomposed; and the biliary salts, in this passage down the alimentary canal, must be absorbed. It is true that these salts cannot be detected in the blood coming from the intestines, but we cannot detect the pancreatine of the pancreatic juice, the pepsin or lactic acid of the gastric juice in the portal blood, yet these are absorbed by the mucous membrane of the intestinal tube, changed by their union with the elements they have digested. It is probable that an analogous change takes place in the glyco-cholate and tauro-cholate of soda, which prevents them from

being detected in the blood by the ordinary tests. These facts, also, place the bile among the secretions.

On the other hand, cholesterine pre-exists in the blood, having been absorbed by this fluid from certain parts of the system, is carried to the liver, and here separated for the sole purpose of being discharged from the body. The same general remarks apply to this substance as to the urea. This places the bile among the excretions.

The flow of the secretions is intermittent. This is not absolutely true of the bile, but the discharge of this fluid is remittent. Dr. Dalton[1] has reported a series of interesting experiments upon an animal with a duodenal fistula. In this observation ten grains of dry biliary matter were discharged into the duodenum of a dog weighing thirty-six and a half pounds, immediately after feeding. At the end of the first hour it had fallen to four grains; it continued at three and a half to four and a half grains up to the eighteenth hour, when the quantity was inappreciable; at the twenty-first hour it was one grain, the twenty-fourth, three and a quarter grains, and the twenty-fifth three grains. The fluid was drawn for fifteen minutes each time, evaporated to dryness, extracted with absolute alcohol, precipitated with ether, the ether precipitate dried, and weighed as representing the quantity of biliary matter present. These experiments apply to the time when the bile is discharged into the intestine; but as most animals have a gall-bladder, which collects the bile as it is secreted, it does not show when this fluid is formed by the liver. Schwann, Bidder and Schmidt, Arnold, Kölliker, and Müller, have made experiments bearing upon the latter point, by ligating the ductus communis choledochus and making a fistula into the fundus of the gall-bladder. The experiments of these observers vary somewhat with regard to the time when the secretion of the bile is at its maximum. In the animal referred to on page 308, in which a fistula was made into the fundus of the gall-bladder, the bile was collected for thirty minutes immediately after feeding, one hour after, and then at intervals of two hours during the remainder of the twenty-four hours. The specimens of bile thus collected were carefully weighed, evaporated to dryness, and the proportion of dry residue taken. The accompanying table shows the results of these observations, which were made twelve days after the operation, when the animal, which weighed originally twelve pounds, had lost two pounds. His appetite was ravenous at the time of the experiment.

[1] Dalton on the Constitution and Physiology of the Bile. Loc. cit.

Table of the variations of the bile in the twenty-four hours. At each observation the bile was drawn for precisely thirty minutes. Dog with a fistula into the gall-bladder. Weight ten pounds.

Time after Feeding.	Fresh Bile.	Dried Bile.	Percentage of Dry Residue.
	grains.	*grains.*	
Immediately . . .	8.103	0.370	4.566
One hour	20.527	0.586	2.854
Two hours	35.760	1.080	3.023
Four hours	38.939	1.404	3.605
Six hours	22.209	0.987	4.450
Eight hours	36.577	1.327	3.628
Ten hours	24.447	0.833	3.407
Twelve hours . . .	5.710	6.247	4.325
Fourteen hours . . .	5.000	0.170	3.400
Sixteen hours . . .	8.643	0.309	3.575
Eighteen hours . . .	9.970	0.277	2.778
Twenty hours . . .	4.769	0.170	3.565
Twenty-two hours . . .	7.578	0.293	3.866
Twenty-four hours . .	15.001	0.885	5.233

This table shows a regular increase in the quantity of bile discharged from the fistula from the time of feeding up to four hours after. It diminished at the sixth hour, rose again at the eighth hour, but then gradually diminished to the fourteenth hour. We then have a slight increase the sixteenth and eighteenth hours, and the twentieth hour it falls to its minimum. It then increased slightly the twenty-second hour, and mounted considerably the twenty-fourth hour, when the observations were concluded. Disregarding slight variations in the quantity, which might be accidental, it may be stated in general terms, that *the maximum flow of bile from the liver is from the second to the eighth hour after feeding; during which time it is about stationary. In this experiment it was at its minimum the twentieth hour after feeding.* This observation agrees with those of Bidder and Schmidt as regards the time when the bile begins to increase in quantity ; but these observers state that it is at its maximum at the twelfth to the fifteenth hour. This, however, is not material to the question now under consideration. We wished to establish the fact that the quantity of bile secreted varied considerably during the various stages of the digestive act; a character which approximates it to other secretions. The flow of the bile is not intermittent, because it contains a substance which is excrementitious; but it is remittent, having a definite relation to the digestive act, because it contains substances which are recrementitious and are in some way connected with the process of digestion.

The continuous, though remittent, flow of the bile allies it with the excretions. There is no time, in health, when the bile is not separated from the blood. In animals that go through the process of hibernation, the bile continues to be secreted, though no food is taken into the alimentary canal. Nutrition, though much diminished in activity, goes on during this state,

and the urea and cholesterine must be separated from the blood. The forma-
tion of the bile and urine, therefore, is not interrupted. The bile is secreted
also in the fœtus, before any nourishment is taken into the alimentary canal,
when none of the other digestive fluids are formed. This character it has
in common with the urine, and this places it among the excretions.

The elements of secretion never accumulate in the system when the secre-
tion is interfered with; while the elements of excretion do accumulate in the
blood in such cases, and produce their toxic effects. Experimenters have
often analyzed the blood for the biliary salts in cases of serious disease of
the liver, marked by symptoms of bile poisoning, regarding these as the
only important elements of the bile; but they have never been detected. I
have made no observations on this point, for the fact that the glyco-cholates
and tauro-cholates of soda do not accumulate in the blood in diseases of the
liver has long been settled. This stamps these substances as products of
secretion; but we will see when some of the pathological conditions of the
cholesterine are taken up, that this substance does accumulate in the blood
when the functions of the liver are seriously interfered with, which marks
it as a product of *excretion.*

It seems to me that enough has been said with regard to the function of
the bile to convince the reader that this complex fluid has two important
elements which have two separate functions.

First. *It contains the glyco-cholate and tauro-cholate of soda; which are
not found in the blood, are manufactured in the liver, are discharged
mainly at a certain stage of the digestive process, are destined to assist
in some of the nutritive processes, are not discharged from the body, and,
in fine, are products of secretion.*

Second. *It contains cholesterine; which is found in the blood, is merely
separated from it by the liver, and not manufactured in this organ, is
not destined to assist in any of the nutritive processes, but merely sepa-
rated to be discharged from the body, and is a product of excretion.*

These two propositions, and more especially the second, being established,
it becomes our task now to follow out the cholesterine after it has been
discharged from the liver into the small intestine. If it be discharged from
the body it must be by the rectum, and to complete the history of choles-
terine we find it necessary to study the feces.

The Feces.—It is not my object to consider all the effete matters which
go to make up the feces, though it must be acknowledged that our infor
mation on this subject is very limited. Following the cholesterine in its
passage down the alimentary canal has opened a new subject for investiga-
tion, which it will be impossible to do entire justice to in this paper. There
is a field for a long series of investigations into this part of our subject,
which I hope to be able to cultivate to some extent in the future, and add
something to the history of the substance we have been considering. At
present I shall only endeavour to demonstrate the fact that cholesterine, in

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a modified form, is discharged with the feces, and not attempt to treat of the conditions which modify the excretion of this substance (upon which as yet I have no data), which are of the last importance to the practical physician.

It is stated by some of the most reliable authors on physiology and physiological chemistry that cholesterine is found in the fecal matters. Robin and Verdeil say, "*Ce principe immédiat se trouve à l'état normal dans le sang, la bile, le foie, le cerveau, les nerfs, le crystallin et les matières fécales.*" Many other authors refer to it as found in the feces, and it was with that belief, that, in the experiments which form the basis of this article, I deferred my analyses of the feces till I had completed the observations on the blood, and then analyzed them, satisfied that I would find cholesterine, with the view to determine the variations, etc., in its quantity. When after a careful and prolonged examination of many specimens of feces I was unable to extract any cholesterine, I endeavoured to ascertain what observer had established its presence. Though it is mentioned by so many as present in the feces, I could find no mention of any one who had established this point; and in some of the analyses of Simon, I found that he had noted its absence in certain specimens of feces. I found also that Marcet, who published some elaborate analyses of the feces in the *Philosophical Transactions*, in 1854 and 1857, noted the absence of cholesterine in the normal feces of the human subject. We have already seen how conclusively the experiments on the blood from various parts of the system point to the excrementitious character of the cholesterine, showing us even in what part of the system it is found, and where it is eliminated; but it is undoubtedly one of the most important characters of an excretion that it should be discharged from the body, and I was unable for a time to convince myself that it was discharged. After evaporating the feces to dryness, pulverizing, extracting thoroughly with ether, decolorizing with animal charcoal, evaporating the ether and extracting the residue with boiling alcohol, I allowed the alcohol to evaporate, added a solution of caustic potash, and kept the mixture at a temperature near the boiling point for three and a quarter hours. The potash was then carefully washed away in a filter, the residue redissolved in ether and extracted with hot alcohol as before, and the alcoholic extract set aside to evaporate. A number of days passed without any signs of crystallization. The residue was, of course, non-saponifiable; but it differed from the cholesterine by being melted at a much lower temperature, though it presented the red colour with sulphuric acid which is said to be characteristic of the latter substance. It was examined carefully with the microscope daily, and after five or six days, to my great satisfaction, crystals began to form; but they were at first so indistinct that their form could not be clearly made out. These crystals, however, increased in size and number, and in a short time presented all the characteristics of *seroline*. In about ten days the whole mass had crystallized, making one of the most

superb exhibitions of crystals that could be imagined. The seroline crystallizes in the form of delicate transparent needles, which have a beauty under the microscope which could be but poorly imitated by the most delicate steel plate engraving. This substance, from its being found in such large quantity in the feces, I have spoken of as *stercorine*.

Before taking up the changes which the cholesterine undergoes in its passage down the alimentary canal, I will say a few words with regard to the stercorine, which will play an important part in this connection.

STERCORINE.

The stercorine has already been referred to and delineated in the analyses of various specimens of blood for cholesterine. It was discovered by Boudet, and described by him under the name of seroline, in an article published in the *Annales de Chimie et de Physique*, in 1833, as a principle found in the serum of the blood. Up to the present time, this is the only situation in which it has been found, and here in such an excessively minute quantity that enough has never been obtained for ultimate chemical analysis. With regard to its function nothing whatever has been known. Robin thus speaks of it: " *On ne sait pas comment se forme la séroline, ni quel est son rôle physiologique.*"[1]

Chemical characters.—This substance, like cholesterine, is a non-saponifiable fat. It has never been obtained in sufficient quantity for ultimate chemical analysis ; but as in its decomposition it disengages a little ammonia, it is supposed by Verdeil and Marcet to contain nitrogen.[2] The evidences of this ingredient are very slight, and its existence is doubtful. It is neutral, inodorous, insoluble in water, soluble in ether, very soluble in hot alcohol, but almost insoluble in cold. It is not attacked by the caustic alkalies, even after prolonged boiling. When treated with strong sulphuric acid it strikes a red colour, similar to that produced by the sulphuric acid and cholesterine. According to Lehmann it melts at 96° 8' Fahr., and on the application of strong heat may be distilled without change. Boudet extracted it from the serum of the blood, by evaporating it, boiling the residue with water, and evaporating again, taking up the residue with boiling alcohol, which deposited the crystals on cooling. •

Form of its crystals.—Boudet describes the crystals thus obtained as filaments, with varicosities here and there, which gave them a beaded appearance. Lecanu also observed this peculiarity. In the atlas of Robin and Verdeil's *Anatomical Chemistry* we have a beautiful representation of the crystals of seroline from the blood. These observers have not noticed the beaded appearance mentioned by Boudet, but represent the crystals in

[1] Robin and Verdeil, Chimie Anatomique et Physiologique, tome iii. p. 66.
[2] Cours de Physiologie fait à la Faculté de Médecine de Paris. Par P. Bérard, Professeur de Physiologie, &c., tome iii. p. 118. Paris, 1851.

the form of delicate transparent needles, of variable size, some very small and others quite wide, terminating in a fine pointed extremity, which in some of the wider crystals is bifurcated, or even trifurcated, with the edges of the larger crystals frequently split, as it were, into delicate filaments. The smaller crystals frequently arrange themselves in a fan shape. Robin and Verdeil attribute the beaded appearance mentioned by Boudet and Lecanu to the presence of little globules of fatty matter mixed with the crystals. This seems probable, for we shall see when we examine the process of extraction employed by Boudet, that he probably did not succeed in obtaining it in a pure form. The appearance of these crystals has already been given in some of the diagrams of cholesterine, especially in Figs. 2, 6, 7, and 9. I have been able to follow the process of crystallization in the specimens extracted from the feces from its commencement, and have found that the splitting of the ends and edges of the crystals did not take place at first. The needles which were first found had regular borders and single pointed extremities; but after a few days they split up in the manner described and figured by Robin and Verdeil. (See Figs. 14 and 15.)

Situations.—Up to this time the seroline (or stercorine) has only been found in the serum of the blood, and there in but very small quantity, the proportion being, according to the analyses of Becquerel and Rodier, 0.020 to 0.025 of a part per 1,000 parts of blood. They have seen it mount up to 0.060 parts, and descend to a quantity almost inappreciable.[1]

Process of extraction.—In the first observations I made on the blood this substance was observed before the cholesterine. In these observations the blood was dried, pulverized, extracted with ether, the ether evaporated, the residue extracted with boiling alcohol, and then a solution of caustic potash added, which remained on the specimens for a number of days. In all the subsequent analyses of the blood the cholesterine was extracted perfectly pure, and *no stercorine whatever was observed.* The following was the difference in the modes of analysis. In the latter case the solution of potash was not allowed to remain on the specimens more than an hour or two; but was washed away, and the residue, which was left on the filter, redissolved in ether. The failure to detect the stercorine in all the later observations on the blood, which are twenty-four in number, inclines me to the opinion that it does not primarily exist in that fluid; and that when it has appeared in the extract it has been due to a transformation of a portion of the cholesterine. This view seems the more probable, as I have definitely ascertained by observations on the feces, which will be detailed farther on, that the cholesterine is capable of being changed into stercorine, and that this change actually takes place before it is discharged from the body. In my observations on the blood no attempt was made to get rid of this substance,

[1] Traité de Chimie Pathologique Appliquée à la Médecine Pratique. Par M. Alf. Becquerel and M. A. Rodier, p. 62. Paris, 1854.

and *though it is soluble in the menstrua which were used to extract the cholesterine, and not destroyed by any of the means that were employed to purify the cholesterine, it never appeared in the extract.* In these experiments the study of the stercorine in the blood has not been attempted; and though it is not possible to state at present how the cholesterine was transformed in the first observations, it seems most rational to suppose, in endeavouring to explain its absence in the twenty-four succeeding specimens of blood which were examined, that such a change had taken place.

I am inclined to the opinion, then, though I cannot state it positively, that the element under consideration does not exist in the blood as a proximate principle, but is formed from the cholesterine, in some unexplained way, by the processes which have been used for its extraction.[1] This transformation does not take place during the extraction of this substance from the feces, because I have in but a single instance been able to extract cholesterine by the processes which are successful in obtaining it in other situations in which it exists, including the meconium.

The stercorine may be extracted from the feces in the following way : The feces are evaporated to dryness, pulverized and treated with ether, which should be allowed to remain from twelve to twenty-four hours, protected from evaporation. The ether is then separated and decolorized by filtration through animal charcoal, fresh ether being added till the original quantity has passed through. It is impossible to decolorize the solution entirely, but it should be made to pass through of a very pale amber tinge and perfectly clear. The ether is then evaporated and the residue extracted with boiling alcohol. The alcohol is then evaporated and the residue treated with a solution of caustic potash, at a temperature a little below the boiling point, for from one to two hours. This dissolves all the saponifiable fats, and the solution is then largely diluted with water, thrown on a filter, and washed till the fluid which passes through is perfectly clear and neutral. The filter is then dried at a moderate temperature, and the residue washed out with ether, which is evaporated, extracted with boiling alcohol, and evaporated again. The residue is composed of pure stercorine.[2] The extract thus obtained is a clear, slightly amber, oily substance, of about the consistence of the ordinary Canada balsam used in microscopic preparations, and in four or five days begins to show the characteristic

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[1] As we have no ultimate analysis of this substance, it is impossible to enter into any chemical speculations with regard to the change from cholesterine, as we may in the instance of the creatine and creatinine, or the urea and carbonate of ammonia.

[2] As this substance is said to be volatilized at a high temperature, it is important, in our examination, to avoid as much as possible the application of heat. Large quantities of it are extracted from the feces after evaporation over an ordinary water bath, but it might be better to evaporate the excrements at a lower temperature.

crystals. These are at first few in number; but soon the entire mass assumes a crystalline form. In a specimen which I have extracted from the feces I have 10.417 grains, consisting, apparently, of nothing but crystals. If the extract be evaporated in a very thin watch-glass it may be examined with the microscope daily, and the process of the formation of the crystals observed. These crystals, after they are fully formed, may be examined satisfactorily with a half or quarter inch objective.

History of seroline.—Very little is to be said with regard to the history of this substance. Boudet first described it in 1833.[1] Lecanu confirmed these observations in 1837.[2] Since then it has been studied by Becquerel and Rodier,[3] Chatin and Sandras,[4] W. Marcet and Verdeil.[5] Gobley states, in an article published in the *Journal de Chimie Médicale*, that the substance described by Boudet is not an immediate principle but a mixture of several substances, confounding it, however, with cholesterine.[6] Robin and Verdeil adopt this view, but consider it entirely different from the cholesterine.[7]

This element, existing, as it does, in large quantities in the fecal matter, must take its place among the important excrementitious substances discharged from the organism, not second in importance even to the urea. It is a curious fact that while the urea was known as an ingredient of the urine long before it could be demonstrated in the blood, taking its name from that fluid, we have the stercorine, an excrement of great importance, discovered in the blood and never till now recognized as an excrement and an ingredient of the feces, taking a name from the serum of the blood, which does not indicate at all its excrementitious properties nor the situation in which it is found in greatest abundance. As seroline has been heretofore a substance of very little prominence, and as it probably does not exist normally in the serum of the blood, and if at all, in insignificant quantity, the application seems a misnomer. We want a name which will indicate its excrementitious properties, and the channel by which it is evacuated, and I have adopted the name STERCORINE[8] as more appropriate and more suggestive of its properties, as it is undoubtedly the most important excrement discharged by the anus.

The questions which now arise with regard to this substance open a field of inquiry too extensive, by far, to be thoroughly investigated in the

[1] Boudet. Loc. cit.

[2] Lecanu. Études chim. sur le sang humain, thèse. Paris, 1837, page 55.

[3] Becquerel and Rodier. Recherches relatives à la comp. du sang. (Comptes Rendus. Paris, 144, tome xix. p. 1084.)

[4] Chatin et Sandras. Gaz. des hôpit., 1849, page 289.

[5] Bérard. Loc. cit.

[6] Gobley. Sur les matières grasses du sang. (Journal de Chimie Médicale, 1851. Paris, page 577.)

[7] Robin et Verdeil. Loc. cit.   [8] From *Stercus*, ŏris, dung.

time that could be devoted to this subject, or to be discussed in the limits
of this paper. We wish to know the entire history of this product; the
quantity discharged in twenty-four hours; variations that may take place
with season, age, sex, diet, digestion, &c.; and more especially, the modifi-
cations which occur in its discharge in connection with diseased conditions.
These points are of great importance, but require a long and laborious
series of investigations for their elucidation. What has been done in a
measure for the *urea* must be done for the *stercorine*, before we can arrive
at a precise idea of its relations to disease. For this purpose a large num-
ber of quantitative analyses of healthy feces must be made and compared
with similar analyses in different diseases. At present I have only instituted
a sufficient number of examinations to substantiate the statements I have
made with regard to the formation and discharge of this substance, and
added a few examinations of feces in disease which bear upon the same
points. I hope at some future time to go more fully into the study of the
feces, and contribute something towards the elucidation of some of the
questions which naturally arise. In the mean time I present the following
observations on the stercorine as it appears in the feces.

Exp. 9. Seven and a half ounces of feces, perfectly normal in appear-
ance, and being the entire quantity passed in the morning at the regular
time for an evacuation, were taken from a healthy male, twenty-six years
of age. After being evaporated, and pulverized finely in an agate mortar,
the residue weighed 2 oz. 57.313 grains. A small quantity was then ex-
tracted with alcohol, the solution being of a yellow colour, and about six
times its volume of ether added. The ether was filtered after standing for
fifteen minutes, the filter washed with distilled water, and the solution
tested with Pettenkoffer's test for the biliary salts. *None of these salts
were present.*

A watery solution was then made of another portion, which was filtered
and tested with nitric acid, but failed to show the reactions of the colour-
ing matter of the bile.

The dry residue was then treated with five fluidounces of ether for
twenty hours, when it was filtered through animal charcoal, fresh ether
being added till the fluid which passed through made five ounces. It came
through perfectly clear and of a very light golden tinge. It was then
evaporated, leaving a golden yellow fat with a number of whitish resinous
masses. It was then extracted with f℥iss of boiling alcohol, which
removed everything but a small quantity of bright yellow oil, and filtered
while hot. It became turbid on cooling, and was set aside to evaporate.
Both the ethereal and alcoholic extracts had a very offensive rancid odour.
The residue, after the evaporation of the alcohol, consisted of a consider-
able quantity of fat of a yellowish colour and a consistence like thick tur-
pentine. It was then treated with a solution of caustic potash, kept near
212° for about thirty minutes and allowed to stand for twenty hours. At
the end of that time a large quantity of fat floated on the top of the fluid
not at all affected by the alkali. It was then largely diluted with distilled
water filtered and washed, the filter dried, and the residue redissolved in
ether. This ethereal solution was evaporated and the residue extracted
with boiling alcohol as before. After the alcohol had evaporated, a small

quantity was treated with sulphuric acid which produced a peculiar red colour similar to that produced when the acid was added to a specimen of cholesterine, extracted from the blood and used for purposes of comparison.

Five days after, the specimen was examined with a $\frac{4}{10}$th inch objective, and *presented some crystals which looked like seroline;* but it was impossible, on account of the thickness of the glass capsule to apply a sufficiently high power to make this certain. Some long, pale, radiating crystals were observed, composition unknown, but they were not the crystals of excretine described by Marcet.[1] The specimen was treated again with a solution of caustic potash and kept at nearly the boiling point of water for three and a quarter hours, most of the fat floating on the top of the fluid in white flakes and yellow drops, but a considerable quantity undergoing saponification, as evidenced by the colour of the potash solution. The potash was then removed by filtration, the residue dissolved in ether and extracted with boiling alcohol as before.

Four days after the evaporation of the alcohol a large number of the characteristic crystals were formed. These did not have the split extremities and edges noted by Robin, but terminated in a single point, and had regular borders ; these crystals are represented in Fig. 14.

In a few days the entire mass had assumed a crystalline form, and the crystals then presented split extremities and borders such as are mentioned by Robin. (See Fig. 15.)

The quantity of the stercorine was 10.417 grains.

Exp. 10. Another analysis was made of the feces from the same individual. During the experiment a large quantity was unfortunately lost, and the examination, therefore, was not quantitative. The presence of stercorine was established.

Exp. 11. The feces of the dog from which blood of the carotid and

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[1] Marcet, in two papers published in the *Philosophical Transactions,* for 1854 and 1857, describes a new proximate principle in the feces which he calls Excretine. This he obtains in the following way : He first treats the feces with boiling alcohol till nothing more can be extracted. A sediment deposits from the alcohol on cooling. The alcoholic solution is acid. Milk of lime is added to the solution, which gives a yellowish brown precipitate, leaving a clear, straw-coloured fluid. The precipitate is then collected on a filter, dried, afterwards agitated with ether, and filtered, forming a clear yellow solution. In from one to three days beautiful silky crystals collect in masses, or tufts, adhering to the sides of the vessel, throwing out ramifications in every direction. These, viewed under the microscope, are in the form of acicular, four-sided prisms, and this substance is called by Dr. Marcet, Excretine, and is found nowhere but in the feces. It is soluble in ether and hot alcohol, sparingly so in cold alcohol, and insoluble in hot or cold water. It does not crystallize from an alcoholic solution on cooling, but crystallizes from ether. When suspended in boiling water it fuses into resinous masses, and floats on the top. Its fusing point is 203° to 205° Fahr. It may be boiled for hours with potash without undergoing saponification.

In the article published in 1857, Dr. Marcet gives the composition of the Excretine $C^{78} H^{78} O^2 S^1$.

There is no similarity between the form of the substance described by Marcet and the stercorine. Its high fusing point, 203° to 205° Fahr., and its crystallization from an ethereal solution, also serve to distinguish it from the stercorine, which fuses at 96°.8 Fahr., and does not crystallize in an ethereal solution.

internal jugular on one side had been taken fifteen days before, the animal having entirely recovered, were examined. The analysis was not quantitative. The feces were treated in the way already described, and the presence of stercorine determined.

Exp. 12. A specimen of feces voided by a healthy dog, fasting, was examined in the usual way for stercorine. *After the final extract had evaporated, it was examined microscopically, and found to contain, in addition to the stercorine, a considerable quantity of cholesterine, crystallized in beautiful tablets. This is the only examination of feces in which I have found cholesterine.* The proportion of stercorine and cholesterine was as follows :—

Quantity of feces . . . . 137.513 grains.
Stercorine with a little cholesterine . . . 0.216 "

These examinations of the feces in health show that they invariably contain a non-saponifiable fatty substance known under the name of *seroline*, but which I have called *stercorine*. In but one of these analyses, the last, did I find any cholesterine, though the first were originally undertaken with a view to the extraction of this substance.

The stercorine has never before been detected in the feces, and, as far as my knowledge of its physiological properties is concerned, may be considered a new substance; the discovery of which, in this situation, marks it as one of the most important of the products of destructive assimilation. The next question which arises, then, is with regard to its origin.

Origin of the stercorine.—In our study of the chemical properties of this substance, we have already seen that it is one of the non-saponifiable fats, having many characters in common with the cholesterine. It has been described, under the name of seroline, as existing in the blood, in very minute quantity, but does not exist in any of the fluids which are poured into the alimentary canal. The cholesterine, however, which it so closely resembles, is one of the constituents of the bile. The fact that the cholesterine is discharged into the small intestine, and not usually found in the evacuations, while stercorine is abundant, would at once point to a possible connection between these two substances. In most cases, in health, cholesterine disappears, and stercorine is found; but in some rare instances, as in the single examination of dogs' feces, Exp. 12, the two substances coexist in the evacuations, the stercorine, in the example just mentioned, in much the greater quantity. The question then arises : Is the cholesterine capable of being converted into stercorine, and does the latter substance originate from a transformation of the cholesterine of the bile ? Before we treat of this subject experimentally, let us examine the facts which we already have bearing on this point. No examinations of the feces have ever been made for *stercorine*, but under certain circumstances *cholesterine* has been found discharged by the anus without alteration.

Cholesterine has been detected in the meconium, in the feces of hibernating animals, and occasionally in ordinary feces, though I can find no observation of this kind but the one just recorded.

Meconium.—Cholesterine exists in the meconium in considerable quantity, where it may be seen in tablets by a simple microscopic examination, and from which it may be extracted in quantity, and with great facility. The stercorine, or seroline, has never been mentioned as existing in this situation. In the single examination I have made of the meconium I found an abundance of cholesterine, 6.245 parts per 1,000, but no stercorine. There is no difficulty in explaining the origin of the cholesterine in the meconium. Long before any food is taken into the alimentary canal, and before the exclusively digestive fluids are formed, the bile is formed and discharged. It accumulates in the intestine, with other matters constituting the meconium, and is finally evacuated soon after birth. Hence the cholesterine exists in large abundance ; but when the digestive fluids are secreted, and food is received into the alimentary canal, the cholesterine is lost and the stercorine makes its appearance.

Feces of hibernating animals.—As the excreting function of the liver commences before food is taken into the alimentary canal, so it goes on during the state of hibernation, when the animal takes no food for weeks, or even months. Under these circumstances, the cholesterine is found unchanged in the feces, but it disappears when the animal arouses, and the digestive organs resume their functions.

Normal feces.—In the normal feces the cholesterine is generally absent ; but in Exp. 12, it was found in small quantity, mixed with stercorine. This animal had been certainly twenty-four hours, and probably forty-eight hours, without food. The feces were of normal colour and consistence.

These facts seem to show that before digestion commences, as in the fœtus, and when it is suspended, as in hibernating animals and in Exp. 12, cholesterine passes through the alimentary canal unchanged. But as soon as digestion commences, the cholesterine is lost in the feces, and its place is supplied by stercorine. It seems almost certain, then, that in its passage down the alimentary canal, the cholesterine of the bile is acted upon by some of the digestive fluids and changed into stercorine. This change seems to be incident to the digestive act ; for before digestion commences, or when it is suspended, the cholesterine passes through unchanged. A conclusive observation would be to cut off the bile from the intestines, and consequently the cholesterine, and notice the effect upon the production of stercorine. In a case of jaundice from duodenitis (which will be more minutely detailed in the section on the pathological relations of cholesterine), the necessary conditions for this observation seemed to be fulfilled. The patient suffered from intense jaundice, dependent upon obstruction of the common bile duct from duodenitis. The feces were clay-coloured. After a time, the patient was relieved of the jaundice, and the feces regained their natural colour. While the feces were decolorized, and when the icterus was most marked, it is probable that the bile was entirely cut off from the alimentary canal. This condition was relieved, however, when

the feces regained their colour, and the icterus disappeared. For the purpose of ascertaining the effect of the obstruction to the flow of bile on the stercorine in the feces, and of the re-establishment of the flow, the stools were examined chemically during the jaundice, and after the patient had recovered.

Analysis of decolorized feces.—The quantity of feces examined was 941.4 grains. After evaporation, extraction with ether, and extraction of the residue left after the evaporation of the ether, with hot alcohol, the fat, which was very abundant, was entirely saponified by boiling for fifteen minutes with a solution of caustic potash, *showing that neither cholesterine nor stercorine was present.*

Analysis of feces from the same patient after they had become normal in colour.—This analysis was made nineteen days after the preceding one. The quantity of feces was small. The specimen was treated in the usual way, showing stercorine in the following proportions :—

Quantity of feces . . . . 502. grains.
" stercorine . . . . 0.34 "

Taken in connection with the facts which have already been cited with regard to the discharge of cholesterine by the anus, when digestion is not going on, this observation establishes the origin of the stercorine. *It is produced by a transformation, connected with the digestive act, of the cholesterine of the bile.* When the cholesterine does not find its way into the alimentary canal, as was the case in the first analysis of feces, stercorine is not found in the dejections; when the discharge is re-established, the stercorine reappears.

Comparison of the daily quantity of stercorine discharged, with the quantity of cholesterine produced by the liver.—The quantity of stercorine which I extracted from the regular daily feces of an adult healthy male, was 10.417 grains. As there is no cholesterine found in the dejections, this should represent the entire quantity of cholesterine excreted in the twenty-four hours. A comparison of this quantity with the estimated quantity of cholesterine discharged in the day, shows this to be the case.

Quantity of bile in the twenty-four hours (Dalton) . 16.940 grains.[1]
" " cholesterine at 0.618 pts. per 1,000 (A. Flint, Jr.) 10.469[2] "
" " stercorine discharged (*Id.*) . . . 10.417 "

Difference . . .052

This insignificant difference of .052 of a grain, at once proves the correctness of the estimate of the daily quantity of bile excreted, the accuracy of the estimate of the proportion of cholesterine in the bile, and of the quantitative analysis for the stercorine ; and made, as the three observations were, with-

[1] Dalton's Treatise on Human Physiology, 2d edition, page 171.
[2] See table, page 362.

out the slightest reference to each other, adds the final link to the chain of evidence in support of the view that *the cholesterine, in its passage down the alimentary canal, is converted into stercorine, in which form it is discharged in the feces.*

The history of the cholesterine thus resolves itself :—

1. *Cholesterine is an effete material, produced by the destructive assimilation of nervous matters, and absorbed by the blood.*

2. *It is separated from the blood in its passage through the liver, enters into the composition of the bile, giving this fluid its excrementitious character.*

3. *It is poured with the bile into the upper part of the small intestine, when the process of digestion induces a change into stercorine; in which form it is discharged by the feces.*

4. *Stercorine, the great excrementitious element of the feces, is one of the most important excrements produced by the waste of the system.*

PATHOLOGICAL RELATIONS OF CHOLESTERINE.—With the limited data we have on the subject of the variations in the quantity of cholesterine in health and disease, it is impossible to do more than merely to open the great subject of its pathological relations. To a certain extent, all questions in physiology have for an end the elucidation of points in pathology. The practical physician, who may be the reader of this article, will naturally inquire if the more definite views which we are now enabled to hold with regard to the function of the bile be of any use to him in the study and treatment of disease. It is certain that no addition to our knowledge of the functions of the healthy body is without its bearings on disease, immediate or remote. What may seem to be simply a matter of interest to the pure physiologist, without apparently any practical bearing, is sure at some time to be so connected, perhaps, with other advances, as to be useful to the practitioner. But the pathological relations of an important excretion do not have a practical interest so remote, especially when this function is connected with the liver. Almost from time immemorial, a large number of diseases have been referred to derangement of the liver, and in their treatment, it has been thought of immense importance to promote the secretion of the bile. A certain class of remedies supposed to regulate the function of the bile, has been constantly employed by physicians. At the present day, these ideas have fallen somewhat into disrepute; for the enlightened physician is now accustomed to base his pathological views upon a certain amount of definite knowledge, and it has been found that both the physiology and the pathology of the bile have been very little understood. The older practitioners had, as we have now, a certain class of cases characterized by a general *malaise*, and having indefinite symptoms which were attributed to "biliousness," in which they were in the habit of employing the

cholagogues, with mercury at the head, with undoubted success. It is true that, as our knowledge of disease becomes more accurate, the conditions which were supposed to indicate "biliousness," have become referred to other disorders ; but no great advance has been made in the pathology of the liver, and there are yet many conditions which may be successfully —though empirically—treated, the true character of which is unknown. It is on this obscure subject that it is hoped the preceding physiological investigations will throw some light. To repeat an illustration made use of before, a knowledge of the functions of cholesterine, and its history in the healthy organism, should contribute as much to the pathology of diseases dependent on derangement of this function, as has the development of the functions of the urea for diseases now known to be dependent or uremia.

CHOLESTEREMIA.

In common with other excrementitious substances, which invariably exist in the blood in health, if the function of the eliminating organ be interfered with, accumulation takes place in the blood. This fact has already been incidentally referred to in treating of the properties of the cholesterine which allied it to effete substances. It takes place with the urea ; but cases of uremic poisoning occurred, and patients died in uremic coma, long before the cause of it was understood. It is the same with the bile. Ordinary cases of jaundice, which have been called, by Piorry, cholemia, are not of a dangerous character ; but there are cases in which jaundice, though less marked as regards colour, is a very different condition. Here we have evidently the operation of some poison in the blood, and coma and death from its effects on the brain, follow as in retention of the urea. Pathologists inquire why there is this difference in the severity of cases of icterus ? Chemists have analyzed the blood in the hope of explaining it by the presence of the glyco-cholates and tauro-cholates of soda in the grave cases, regarding them as the only important constituents of the bile. But their failure to detect these substances has left the question still unanswered.

In simple cases of jaundice we have a resorption of the colouring matter of the bile from the excretory passages.

In grave cases of jaundice, which almost invariably terminate fatally, we have a retention of the cholesterine in the blood, or cholesteremia.

I have been forced to make use of cases of disease exclusively in studying this condition, for no one has yet been able, in the larger animals, to extirpate the liver, as we do the kidneys, notice the symptoms of poisoning, and demonstrate the accumulation of cholesterine in the blood. Nor have I yet been able, on account of the insolubility of the cholesterine, to make experiments by injecting it into the circulation. I had, however, an opportunity of making an examination of the blood of a patient in the last stages of

cirrhosis of the liver, accompanied with jaundice, and compare it with an examination of the blood of a patient suffering from simple icterus. Both of these patients had decoloration of the feces ; but in the first, the icterus was a grave symptom, accompanying the last stages of the disorganization of the liver ; while in the latter, it was simply dependent on•duodenitis, the prognosis was favourable, and verified by the result. As icterus accompanying jaundice is of véry infrequent occurrence, I deemed myself very fortunate in having an opportunity of comparing the two cases.

CASE I. *Jaundice dependent on obstruction from duodenitis.*—Mary Bishop, æt. 42, native of Ireland, widow, occupâtion servant, was admitted into the Blackwell's Island Hospital, June 12, 1862, with the following symptoms : Slight febrile movement, with severe pain over the duodenum ; the surface of the body was highly icterosed; the stools were clay-coloured ; urine high-coloured, but not examined for bile ; lungs and heart normal; appetite rather poor; no ascites. The icterus had existed since about May 23, 1862. The patient was confined to the bed.

Dr. Flint, the attending physician, pronounced it a case of icterus dependent on duodenitis.

Treatment.—Laxatives daily, with good diet and a moderate amount of stimulus.

June 21. A small quantity of blood was drawn from the arm for examination, and *June* 23, the feces were collected for the same purpose.

June 27. The patient remains about the same.

July 11. All pain and tenderness over the duodenum have disappeared. She has steadily improved since the last record. The stools have been natural for several days. Though confined to the bed most of the time, she is able to sit up two or three hours daily. The jaundice has been gradually diminishing, and three or four days ago it had entirely disappeared, and is now absent.

July 12. Another specimen of the feces, which was of normal appearance, was taken for examination.

Analysis of the blood for cholesterine.—The blood was examined about sixteen hours after it was taken from the arm. It had entirely separated into serum and clot. The serum was of a bright yellow colour—more markedly bilious than in the succeeding case. It was evaporated, pulverized, and a quantitative analysis for cholesterine made, with the following results :—

Quantity of blood	212.428	grains.
Quantity of cholesterine	0.108	"
Proportion of cholesterine per 1,000 pts. of blood .	0.508	"

CASE II. *Jaundice with cirrhosis.*—Ann Thompson, æt. 39, native of Ireland, occupation servant, was admitted into the Blackwell's Island Hospital June 16, 1862, and gave the following history :—

Three months ago she contracted a severe cold, which was accompanied with swelling of the left hand and of both legs, continuing for eight or nine weeks. At the end of that time, she noticed that the abdomen was increasing in size. She was then very weak, the urine was scanty, bowels regular up to the time when she entered the hospital. She denied having been in the habit of drinking spirit, but acknowledged that she drank beer.

June 18. The surface of the body was very much icterosed, the colour

being very marked under the tongue and in the conjunctiva; the abdomen was full of fluid; pulse 90, small and weak; bowels loose, and the dejections clay-coloured; the urine highly tinged with bile and copious; appetite very poor. She was tapped, and about eight quarts of clear, straw-coloured serum were evacuated. The patient was confined to the bed.

Dr. Flint, the attending physician, diagnosticated cirrhosis.

The treatment consisted of sustaining measures, with stimulants, and the tinct. ferri muriat.

June 21. A small quantity of blood was taken from the arm for examination, and *June* 23, a specimen of the feces was obtained for the same purpose.

The patient died June 27. There were no convulsions, and she was sensible, though in a state of stupor, up to twenty minutes before the fatal termination. The stupor existed three or four days before death. Two days before, she complained of double vision. The icterus was excessive up to the time of her death.

Autopsy.—The abdomen contained about twelve quarts of fluid. The liver was examined; its weight was 3 lbs. 12½ oz. It was very light-coloured, and had something of the "hob-nail" appearance; presenting, in short, the gross characters of cirrhosis. The gall-bladder was very much contracted, and contained only about two drachms of bile. Microscopic examination of the organ showed the liver-cells shrunken. The fibrous substance was increased in quantity, and there were present a large number of rather angular globules of fat.

Analysis of the blood for cholesterine.—The blood was examined about sixteen hours after it was drawn. It had fully separated into serum and clot, and the serum was of a greenish, yellow color. The whole, serum and clot, was then evaporated, pulverized, and a quantitative analysis made for cholesterine in the manner already indicated, with the following results:—

Quantity of blood . . . . 50.776 grains.
Quantity of cholesterine . . . . . . 0.093 "
Proportion of cholesterine per 1,000 pts. . . . 1.850 "

The following table gives a comparison of these results with those obtained in the analyses of the three specimens of healthy blood from the arm, which were examined at the same time, and all five specimens subjected to identical processes.

Table of Quantity of Cholesterine in Healthy Blood, Blood from Simple Jaundice, and Jaundice with Cirrhosis.

HEALTHY BLOOD.	Cholesterine per 1,000 pts.	BLOOD OF JAUNDICE.	Cholesterine per 1,000 pts.
Male, æt. 35 . . . 0.445		CASE I. Simple Jaundice . 0.508	
" " 22 . . . 0.658		" II. Jaundice with Cir-	
" " 24 . . . 0.751		rhosis . . . 1.850	

CASE I. Simple Jaundice. Percentage of increase over minimum
    of healthy blood . . 14.157
    Decrease below maximum . 32.357
CASE II. Jaundice with Cirrhosis. Increase over minimum . 315.730
    Increase over maximum . 146.338

The results of the examination of the blood in these cases of disease are very striking and instructive. We have already seen that the variations in health are very considerable. In the three analyses here noted, the maximum was 0.751, and the minimum 0.445 pts. per 1,000. The conditions which regulate this variation it has not yet been possible to study; but we know enough with regard to it to see that in the examination of blood in disease, the cholesterine must mount considerably above the maximum, or fall much below the minimum, to be considered beyond the limits of health. But in the second specimen of jaundiced blood, the variation from the limits of health is so considerable as to enable us to draw very important physiological and pathological conclusions.

In the first place, what is the bearing of these observations on the *physiology* of cholesterine? As before remarked, no one has been able to remove the liver from a living animal, and notice the effect upon the quantity of cholesterine in the blood.[1] This experiment, if it were possible, and if it showed that the cholesterine increased in quantity, and killed the animal, would be positive proof that it was an excrementitious substance, and that it was removed by the liver. But while the experimental physiologist contributes much to the information of the pathologist by artificially producing abnormal conditions, pathology furnishes a multitude of useful experiments of Nature, if we may so term them, which are invaluable to the physiologist. In the present instance, cases of disease of the liver present a condition which we are not at present able to imitate by experiments on the lower animals. Disorganizing disease of the liver must interfere with its excretory function, as Bright's disease does with the elimination of urea; and if cholesterine be an excrementitious substance to be removed by the liver, when the liver is seriously affected with structural disease, we will have an accumulation of it in the blood. *This, if fully established, is positive proof of the character of cholesterine and the function of the liver connected with its elimination.*

What do we learn then by a comparison of the blood in Case II. of jaundice dependent on cirrhosis, with healthy blood and a study of the history of the case?

The cholesterine, in this instance, is enormously increased in quantity, 315.730 per cent. over the minimum, and 146.338 per cent. over the maximum. The case, as far as symptoms are concerned, was of a very grave character. The patient not only suffered from an accumulation of fluid, but there was evidently a poison in the system. The patient died after

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[1] Müller, Kunde, and Moleschott, have succeeded in extirpating the liver from frogs, and keeping them alive for two or three days—Moleschott preserving them for several weeks. These observations were made with reference to the accumulation of the biliary salts, and of the bile pigment in the blood, their attention not having been directed to cholesterine. A series of experiments on frogs was commenced by the writer, but they promised to be so prolonged that they were deferred.

three or four days of stupor, and, on post-mortem examination, the liver was found disorganized. There was a deficient secretion of bile, and had been for a long time, for the gall-bladder was very much contracted, and the stools were clay-coloured. In short the patient died of *cholesteremia ;* and the fact that this condition can exist is a proof of the excrementitious function of the cholesterine, as uremia, as a toxemic condition, presupposes that urea is an excrement.

Physiologically this case fulfils the essential condition of excrementitious substances ; namely, accumulation in the blood when the eliminating functions of the excretory organs are interfered with. The liver became so disorganized that its functions were seriously embarrassed, and the quantity of cholesterine in the blood increased to an enormous extent.

The *pathological* deductions from the facts which have been elicited by the examination of the blood in these cases seem to me of great importance. The literature of diseases connected with disorders of the liver is full of theories, more or less plausible, to explain certain conditions which have long been established by clinical observation. We have cases of simple jaundice which are not dangerous to life, and sometimes, though the icterus be excessive, run a certain course without even interfering with the ordinary avocations of the patient. Again, we have jaundice which is invariably fatal. That disease described by Frerichs under the name of acute atrophy of the liver, and called by some acute jaundice, is one of the most serious diseases of which we have any knowledge. The existence of this great difference has led clinical observers to attribute the mild cases to simple resorption of the *colouring* matter of the bile, and the severe cases to a retention or resorption of some of its more important constituents ; especially as it has also been observed that the symptoms which characterize the latter condition occasionally occur in structural diseases of the liver without any discoloration of the skin. But the pathology of this disease has been entirely unknown. It has been thought that in such cases some of the elements of the bile should exist in the blood. Frerichs says : " In the same way that urea accumulates in large quantity in the blood in granular degeneration of the kidneys, so ought the biliary acids and bile-pigment to accumulate in the blood in cases of granular liver. Repeated observations have proved that this is not the case."[1] Experiments on animals have been followed with like results. The frogs that were kept alive by Moleschott for weeks after the removal of the liver did not present a trace of any of the biliary salts or pigment in any part of the system, showing that these matters are manufactured in the liver. This obscurity, which leads to all sorts of theories with regard to liver pathology, must exist as long as our knowledge of the physiology of the bile is so indefinite. If ob-

[1] A Clinical Treatise on Diseases of the Liver, by Dr. Fried. Theod. Frerichs, Prof. of Clinical Medicine, &c., Berlin. Translated by Charles Murchison, M. D. The New Sydenham Society, London, 1860, vol. i. p. 83.

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servers had looked for cholesterine—a substance which pre-exists in the blood and is separated by the liver—instead of the biliary salts—which do not pre-exist in the blood, are manufactured in the liver, as these experiments tended to show, and are peculiar to the bile—they would have met with different results. The very fact that the biliary salts are peculiar to the bile, and found in no other fluid, should have led them to disregard this substance in their analyses of the blood, because this stamps it as a secretion and distinguishes it from the excretions ; they should have looked for some substance which exists in the blood as well as the bile, an indispensable condition of an excretion, and this substance is the cholesterine.

Understanding, as we now do, the physiological relations of the cholesterine, we may divide jaundice into two varieties : simple *Icterus*, or yellowness, and a condition which I have called *Cholesteremia*. We may have, also, the latter condition unaccompanied by discoloration of the skin.

Simple icterus.—In simple icterus we have a resorption of the colouring matter from the biliary passages. As it has been proven that the colouring matter of the bile appears first in the liver, when it exists in the blood, it is not due to accumulation, but to resorption. In these cases the resorption is generally dependent on obstruction from some cause, by means of which the bile is confined. The patient suffers only from the disease which causes the obstruction, and from the derangement of digestion which is due to the absence of bile in the intestinal canal. In those cases, in which we have no organic lesion of the liver, there is no danger of absorption of the cholesterine. We have a condition which is analogous to retention of urine. The patient suffers simply from retention of bile in the excretory passages, and cholesteremia is no more to be expected from obstruction of the bile duct without structural changes of the liver, than uremia is to be looked for in vesical retention of urine without organic change in the kidneys. Excrements are not reabsorbed, though they may be retained in the blood.

The quantity of cholesterine in the blood is not necessarily increased in simple icterus, for the liver is still performing its function of eliminating it, and when once separated from the blood it is not taken up again. The analysis of the blood in Case I. indicated a proportion of 0.508 parts per 1,000, which is within the limits of health ; a little below the mean, probably on account of the somewhat enfeebled condition of the patient.

The feces may or may not be decolorized, this depending on the extent of the obstruction to the passage of bile into the intestine. The obstruction to the flow of bile is frequently removed before the system has time to remove the coloration of the skin, and the feces become normal while the patient is icterosed. In some instances there is no change in the appearance of the dejections during the course of the disease. When the dejections are entirely decolorized there is an absence of the *stercorine*, into which the cholesterine is transformed before it is discharged, with an ab-

normal quantity of fat which has passed through undigested.[1] This element reappears in the feces when the flow of bile is re-established and they assume their normal colour.

The two following analyses were made of the feces in Case I.; one, when they were entirely decolorized, and the patient was very much icterosed, and the other, when she had recovered, and the dejections had assumed their natural appearance.

Feces of Case I. Jaundice dependent on duodenitis. First analysis.— The feces were clay-coloured, and apparently destitute of bile. They weighed 941.4 grains. They were evaporated to dryness without difficulty, pulverized, digested with f℥iij of ether for twenty hours, filtered through animal charcoal, evaporated and extracted with hot alcohol. The fatty residue after evaporation of the alcohol was very abundant.

The residue was then treated with a solution of caustic potash and exposed to a gentle heat. In fifteen minutes it became entirely saponified, forming a clear homogeneous soap with no residue, showing the entire absence of stercorine. The soap was boiled down and moulded into a cake, which I preserved and which weighs 34 grains. The following are the results of the examination :—

Quantity of feces	941.4 grains.
" fat	39.124 "
Percentage of fat	4.144
No stercorine or other non-saponifiable fats.	

Feces nineteen days after. Second analysis.—At that time the patient had entirely recovered from the jaundice, and the feces had regained their natural appearance. A small specimen was taken for chemical examination, which was done, employing the process already described for the extraction of stercorine, with the following results :—

Quantity of feces	503. grains.
" stercorine	0.340 "

Cholesteremia with icterus.—In jaundice complicated with blood poisoning we have a very different state of things as regards gravity of symptoms and prognosis. This occurs in acute jaundice, or when it accompanies, and is dependent upon, structural change in the liver, as the jaundice of cirrhosis. The difference in the pathology of these cases, compared with those of simple icterus, has long been recognized; but, as before remarked, analysis of the blood has failed to throw any light on the subject, because chemists directed their attention exclusively to the biliary salts. Frerichs says :—

"I have myself repeatedly examined jaundiced blood, which has been obtained by venesection, or still more frequently, from the heart or venæ cavæ of the dead body, for the biliary acids, and their immediate derivatives; and more recently I have had it examined by my assistant, Dr. Valentin, but always with negative results. No substance could be found in the alcoholic extract of the

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[1] This fact, which has often been remarked, seems to indicate that the bile is actively concerned in the digestion of the fats. I have noticed that dogs with biliary fistulæ, though with a ravenous appetite, refuse to eat fat meat. This disinclination to eat fat has been noticed in cases of jaundice with decoloration of the feces.

blood which yielded any indication, by Pettenkoffer's test for the biliary acids, whether this alcoholic extract was treated directly with sulphuric acid and sugar, or whether, in order to get rid of foreign substances, a watery extract of it was first prepared. This coincides with the experience of most of the older ob-servers."[1]

In cases of blood poisoning by retention and accumulation of elements of the bile in the blood, we have, as the important pathological condition, the great increase in the quantity of cholesterine. The fact of accumula-tion of this substance in the blood in certain cases of icterus, has been no-ticed by Becquerel and Rodier; but they do not connect it with structural change in the liver, and do not explain its physiological or pathological importance. The fact of its accumulation in the blood is strong evidence of its excrementitious function, but this does not appear to have attracted the attention of the observers just mentioned. The following is one of the cases in which increase of the cholesterine was observed by them, the only one in which they allude to its significance, and here merely to state their inability to explain it:—

"The second case is nearly similar, excepting the phlegmasia, which did not exist. It relates to a boy, nineteen years of age, a *limonadier*, affected for some time with a bilious diarrhœa, with fever, and icterus, recently developed and very marked. There existed in the blood of this patient a slight diminution of the globules (136); albumen in normal quantity (71.4); likewise fibrin (2.3); fatty matter sufficiently abundant; seroline in an imponderable quantity; cho-lesterine excessively abundant (0.798); soaps abundant (2.032). *To what cause must we attribute this great quantity of cholesterine? How and why is it con-centrated in the blood in spite of the biliary flux? This is what it is difficult to decide.*"[2]

The acquaintance we now have with the physiology of cholesterine re-moves the difficulty in the explanation of this fact. In Case II. we had the rare complication of jaundice with cirrhosis, the symptoms evidently point-ing to poisoning by retention of some noxious element in the blood. Ex-amination of the blood in this case showed that the cholesterine existed in the proportion of 1.850 parts per 1,000; the minimum of healthy blood being 0.445 and the maximum 0.751 parts. Taking this case as an exam-ple, we have cholesteremia with jaundice presenting symptoms which cha-racterize the retention of bile in the blood, which are already well known, and were established long before we were able to say what element was retained. Cases in which jaundice exists with cholesteremia are so differ-ent from cases of ordinary jaundice that there is no difficulty in making the discrimination by symptoms. When jaundice exists with cirrhosis, it is probable that we always have cholesteremia. In acute jaundice the symp-toms, especially those referable to the nervous system, are so marked that the gravity of the case is easily recognized. I have no doubt but in such cases the cholesterine is immensely increased in the blood, though on ac-count of their rarity I have not had an opportunity of determining this by

[1] Frerichs, op. cit., page 95.

[2] Translated from Becquerel and Rodier, op. cit., page 210. The Italics are my own.

analysis. Icterus with cholesteremia and simple icterus are as distinct from each other as possible. The only feature they have in common is the discoloration of the skin. The simple icterus, which is comparatively harmless, is not liable to run into the more severe variety, which cannot occur without structural change in the liver; while the grave variety occurs when we have evidence of organic lesion of the liver, or presents symptoms from the first which indicate its serious character. The one has no more constitutional danger than exists in a simple case of spasmodic retention of urine, while the other has characters as grave as those which accompany uremic poisoning from disorganization of the kidney.

In these cases the feces may show a very marked deficiency of bile, but this is due to the deficient, but not arrested, secretion of this fluid, while the clay-coloured stools in simple icterus are dependent on the want of discharge of the bile into the intestine. While in the latter instance, as in Case I., we would expect to find an absence of stercorine in the dejections, in the former we would expect to find it, though in greatly diminished quantity. Further examination of the feces in cases of structural disease of the liver will be of immense advantage as indicating, by the quantity of stercorine found, the extent to which the eliminative function of the liver is interfered with.

The following analysis was made of the feces in Case II. of jaundice dependent on cirrhosis.

Feces of Case II. Jaundice dependent on cirrhosis.—The feces were clay-coloured, though it was not quite as marked as in the Case I. of simple jaundice.

The specimen was evaporated with great difficulty. It came down to a black glutinous mass which could not be pulverized. It was treated twice with alcohol, the alcohol evaporated, and once with ether. After the ether had evaporated it was pulverized and analyzed for stercorine, with the following results:—

Quantity of feces . . . . 272.1 grains.
Stercorine . . . . 0.077 "

In this analysis we have a very great diminution of the stercorine in the feces, the normal quantity in the daily passages, according to the single examination I have made, being 10.417 grains. The specimen was the ordinary amount passed daily. It showed that the cholesterine was still eliminated, though not with sufficient activity to prevent its accumulation in the system. This was further evidenced by the post-mortem examination, when the gall-bladder was found contracted, but containing a small quantity of bile.

Examination of the blood and feces of the patient suffering under cholesteremia with jaundice, thus leads to the following conclusions:—

1. *The cholesterine is enormously increased in the blood, showing that the structural change in the liver has interfered with its removal from that fluid.*

2. *The stercorine is correspondingly diminished in the feces, showing that the cholesterine is not discharged in normal quantity into the alimentary canal.*

Cholesteremia without icterus.—In a practical point of view, this condition becomes one which it is very important to be able to recognize ; but it is here that we feel most the necessity of more extended investigations than it has been possible to make. I have been enabled only to open the subject by the analysis of one or two specimens of blood taken from patients who had organic change in the liver, but no jaundice. One of the most familiar of these affections of the liver consists in those changes of structure which are included in the term cirrhosis. It is very unusual to find this associated with jaundice, and we have already seen how serious this symptom is. Frerichs describes a condition which he calls *acholia,* denoting suppression of the functions of the liver. This is the same condition which I have called *cholesteremia,* which expresses the element of the bile which produces the toxic effects, the action of which was unknown to Frerichs, while the term acholia expresses retention of bile without giving us any idea of the active morbific agent. Further investigation will, undoubtedly, establish more fully what the analyses I have made thus far seem to show, namely, that in what Frerichs calls acholia without jaundice, we have the cholesteremic condition we have seen to exist in acholia with jaundice. The following quotation from Frerichs' admirable treatise on the liver, gives an idea of one of the conditions in which we have acholia (or cholesteremia) with or without jaundice.[1]

" Cases have repeatedly occurred to me, in which individuals who for a long period have suffered from cirrhosis of the liver, have suddenly presented a series of symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with noisy delirium, from which they passed to deep coma, and in this state have died. In one case there was spasmodic contraction of the muscles of the left side of the face. In most cases, slight jaundice made its appearance at the same time, and in one instance there were petechiæ. Upon *post-mortem* examination, not the slightest lesion could be detected in the brain, neither were there indications of any acute disease which could account for the derangement of the cerebral functions. The liver, in all cases, presented cirrhotic degeneration in a marked degree, and the glandular cells were for the most part loaded with fat; large quantities of leucine separating from it ; the bile ducts contained only a small quantity of pale bile."

In certain cases of organic lesion of the liver, and probably in all cases accompanied by the grave symptoms mentioned by Frerichs, we have cholesteremia ; but this character does not exist in all cases where the liver is affected, any more than uremia exists in all cases of structural disease of the kidney. Nature not only provides organs which are sufficient for the removal of effete matters from the blood, but provides for conditions in which the function of these organs may be partly interrupted, and yet the excretion go on, a part taking on the function of the whole. One of the kidneys may be removed, and yet the other, increased in size it is true, is

[1] Frerichs, op. cit., page 241.

capable of performing the function of both. The kidneys may be partially disorganized, and yet the sound portion be sufficient for the depurative function, and urea will not accumulate in the blood. So it is with the liver. We see patients with partial disintegration of this organ, as in some cases of cirrhosis, suffering apparently but little inconvenience from the disease, and presenting none of the symptoms of cholesteremia. But when the liver is extensively affected, so much so that it cannot separate the cholesterine effectually from the blood, we have the condition of cholesteremia. I have made an analysis of the blood of two patients affected with cirrhosis, who presented this contrast as regards the symptoms of cholesteremia. In one of them, Case III., there was considerable constitutional disturbance; and in the other, Case IV., the patient was about, and suffered no great inconvenience, though he had been tapped for ascites about thirty times.

Case III. *Cirrhosis with ascites, and considerable affection of the general health.*—Mary Perkins, æt. 23, native of Ireland, prostitute, has been a spirit-drinker for about seven years, about the first of May, 1862, noticed an enlargement of the abdomen, which was accompanied with pain over the region of the liver, when she took to the bed. She states that at that time the stools were dark green. Fluid continued to accumulate in the abdomen, and was drawn off in the hospital (Blackwell's Island), June 25. About six quarts of a clear, straw-coloured serum were removed, but a little was left in the abdomen, as the patient was very weak. The patient improved after the removal of the fluid, which did not reaccumulate in any considerable quantity. The liver was found diminished in size, and from this and other circumstances, the diagnosis was cirrhosis.

June 28. A specimen of blood was taken from the arm for examination. She left the hospital July 6, and was confined to the bed till within a few days of her discharge.

Analysis of the blood for cholesterine.—The blood presented nothing peculiar in its appearance. A quantitative analysis was made for cholesterine, with the following results:—

Quantity of blood	117.193	grains.
" " cholesterine	0.108	"
Proportion of cholesterine per 1,000 parts of blood .	0.922	"

Case IV. *Cirrhosis with ascites, and slight constitutional disturbance.* —Thomas Hughes, æt. about 33, brewer, presented himself at the Long Island College Hospital, July 1, 1862, with Dr. Dugan, of Williamsburg. He confesses to have been in the habit of drinking more or less spirit daily for the past ten years. The abdomen began to swell about eighteen months ago. The ascites was preceded by hæmatemesis, when he vomited an abundance of black, clotted blood. The belly immediately began to swell, and enlarged rapidly. He took hydragogues under the direction of a physician, and the dropsy disappeared, but returned whenever the medicines were discontinued. Œdema of the lower limbs occurred soon after the ascites commenced. He has had recurrence of hæmatemesis twice since the first attack.

He was first tapped two or three months after the affection occurred, and has been tapped about thirty times since. Was tapped last on the 27th

ult. *He is tapped and goes out the next day. He thinks nothing of it, and is always for the time relieved.* He has continued to drink beer daily and some spirit. After tapping his appetite is good, and food occasions no inconvenience. When he is full, food occasions a distressing distension, so that he does not eat freely.

Urine is scanty when the abdomen is full, and free, after tapping.

There is no pain in the belly, or elsewhere. He is about all day, but is not engaged in business. He says he is not very feeble. He presents a notably anæmic aspect.

The abdomen is now moderately full (July 1.) Superficial veins of abdomen much enlarged. Heart appears not enlarged; a feeble systolic murmur over the body of the organ.

Several months before the ascites began, he got into a fracas, and was beaten badly. He was not laid up, but says he did not feel well afterward, and is disposed to attribute his disease thereto.

Advised to continue to tap when the abdomen refills, with tonics, hygienic measures, and abstinence from spirit, continuing the use of ale moderately. (*Private records of Dr. Flint.*)

July 1. A specimen of blood was taken from the arm for examination.

Analysis of the blood for cholesterine.—The blood was treated in the usual way, and a quantitative analysis made for cholesterine, with the following results :—

Quantity of blood . . . . 251.567 grains.
" " cholesterine . . . . . . 0.062 "
Proportion of cholesterine to 1,000 parts of blood . 0.246 "

The following table shows the comparative quantity of cholesterine in these specimens, and in the three specimens of healthy blood.

HEALTHY BLOOD.	Cholesterine per 1,000 pts.	BLOOD OF CIRRHOSIS.	Cholesterine per 1,000 pts.
Male, æt. 35 . . .	0.445	CASE III. Cirrhosis (severe)	0.922
" " 22 . . .	0.658	CASE IV. Cirrhosis (mild) .	0.246
" " 24 . . .	0.751		

CASE III. Cirrhosis (severe). Percentage of increase in cholesterine
over minimum of healthy blood . 107.190
Ditto over maximum . . . 22.769

CASE IV. Cirrhosis (mild). Percentage of decrease in cholesterine
below minimum of healthy blood . 42.469

These two cases present a very striking contrast; and the chemical examination of the blood has shown as marked a difference in the quantity of cholesterine, as in the gravity of the attendant symptoms. It teaches, however, an important lesson. *We do not always have an accumulation of cholesterine in the blood when the structure of the liver is altered; it being requisite that this alteration should involve enough of the organ to interfere with the elimination of this substance.* The quantity may even fall below the natural standard, in a patient who is rendered anemic by the consequences of a cirrhosis, which is not sufficient to induce cholesteremia. The process of nutrition being thereby diminished in activity, the production of this substance, by destructive assimilation, is necessarily dimi-

nished. The cholesteremia may be slight and transient ; for the causes which produce it may be, to a certain extent, temporary. In Case III. we have the patient confined to the bed, suffering acute pain over the region of the liver, in all probability due to a slight degree of inflammation. This interfered with the excretion of cholesterine, and we find its proportion in the blood increased to 22.769 per cent. over the maximum, and 107.190 over the minimum.[1] As the patient was somewhat enfeebled by syphilis before the symptoms of disease of the liver made their appearance, it is probable that the quantity of cholesterine in the blood did not mount up to the highest standard in health. At all events, there was a notable increase even over the maximum quantity. Case IV. is not less instructive. Here we have a patient who has had cirrhosis of the liver, with ascites, for eighteen months, and has been tapped upwards of thirty times. He apparently has suffered from nothing more than the mechanical effects of the liquid, which has interfered at times with digestion, and rendered him anæmic. He is tapped, and immediately relieved, going out the next day. We do not seem to have any interference with the functions of the liver, as far as the symptoms are concerned, other than the mechanical obstruction to the circulation, and the case, in its symptoms, resembles one of those cases of ovarian dropsy where we have the patient carrying about an immense quantity of water, but suffering only from this circumstance, and relieved temporarily when the water is removed. Considering the state of the patient, we should not be surprised to find the cholesterine of the blood not increased, but diminished in quantity ; and we may, I think, come to the conclusion from the symptoms, as well as the analysis of the blood, that though the liver was affected sufficiently to produce obstruction of the circulation, there was not sufficient disease to produce cholesteremia.

It is evident that much more extended observations are necessary in order to establish the clinical relations of cholesteremia without jaundice ; but the case of Mary Perkins shows that this condition does exist, while the case of Thomas Hughes shows that it does not follow structural change in the liver, unless the lesion be extensive. The fact that we may have poisoning of the blood by the retention of a biliary matter, *without discoloration of the skin*, is exceeding important ; and of this there seems to me to be no doubt. When we have a patient who has structural disease of the liver, and presents symptoms of blood-poisoning, he is suffering under *cholesteremia*, though there be no icterus. The cholesteremia may vary in degree from the mildness which characterized Case III., in which it was, perhaps, temporary,[2] to the grave condition mentioned by Frerichs, characterized by noisy delirium and coma, and announcing a speedy fatal termination. When we add to these conditions the cases of what is ordinarily

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[1] Unfortunately the character of the stools was not noted.

[2] The patient having gone out of the hospital, it was impossible to settle this point experimentally.

called biliousness, attended with drowsiness, an indefinite feeling of *malaise*, constipation, etc. (and all this relieved by a simple mercurial purge, which is said to promote the secretion of the liver), cannot we hope that some light will be shed on their pathology by a knowledge that there is a condition called cholesteremia ? As yet this is but speculation ; but the discovery of the important function of cholesterine opens an almost boundless field of inquiry in this direction ; and ere long the physician may talk of "biliousness," and "liver complaint," with some definite ideas of their pathology.

The following table gives the results of the quantitative analyses for cholesterine, which have been referred to in this article.

Table of Quantitative Analyses for Cholesterine.

		Quantity examined.	Cholesterine per 1,000 pts.
		grains	
Human blood from the arm.	Healthy male æt. 35 . .	312.083	0.445
" " "	" " æt. 22 . .	187.843	0.658
" " "	" " æt. 24 . .	102.680	0.751
" " "	Simple jaundice, . .	212.428	0.508
" " "	Cholesteremia with jaundice	50.776	1.850
" " "	Cirrhosis (grave), . .	117.193	0.922
" " "	" (mild), . .	251.567	0.246
" " "	Hemiplegia—		
	Case I. Paralyzed side .	55.458	—
	Sound side .	128.407	0.481
	Case II. Paralyzed side .	18.381	—
	Sound side .	66.396	0.808
	Case III. Paralyzed side	21.824	—
	Sound side .	52.261	0.579
Blood from carotid	}	179.462	0.774
" " internal jugular	} Dog experiment . .	134.780	0.801
" " femoral vein	}	133.886	0.806
" " carotid	} Dog experiment { . .	140.847	0.768
" " internal jugular	{ . .	97.811	0.947
" " carotid	}	143.625	0.967
" " internal jugular	} Dog experiment. . .	29.956	1.545
" " femoral vein	}	45.035	1.028
" " carotid	}	159.537	1.257
" " portal vein	} Dog experiment . .	168.257	1.009
" " hepatic vein	}	79.848	0.964
Human brain (subject killed instantly) . . .		159.753	7.729
" (Case II., killed instantly) . . .		150.881	11.456
Human bile (specimen from Case II.)		224.588	0.618
Crystalline lens (4 lenses from the ox)		135.020	0.907
Meconium		170.541	6.245

CONCLUSIONS.—The observations contained in the preceding article seem to the writer to justify the following conclusions :—

1. Cholesterine exists in the bile, the blood, the nervous matter, the crystalline lens, and the meconium, but does not exist in the feces in ordinary conditions. The quantity of cholesterine in the blood of the arm is from five to eight times more than the ordinary estimate.

2. Cholesterine is formed, in great part if not entirely, in the substance of the nervous matter, where it exists in great abundance, from which it is taken up by the blood, and constitutes one of the most important of the effete or excrementitious products of the body. Its formation is constant, it always existing in the nervous matter and the circulating fluid.

3. Cholesterine is separated from the blood by the liver, appears as a constant element of the bile, and is discharged into the alimentary canal. The history of this substance, in the circulating fluid and in the bile, mark it as a product destined to be gotten rid of by the system, or an excretion. It pre-exists in the blood, subserves no useful purpose in the economy, is separated by the liver and not manufactured there, and, if this separation be interfered with, accumulates in the system, producing blood-poisoning.

4. The bile has two separate and distinct functions dependent on the presence of two elements of an entirely different character. It has a function connected with nutrition. This is dependent on the presence of the glyco-cholate and tauro-cholate of soda, which do not pre-exist in the blood, subserve a useful purpose in the economy, and are not discharged from it, are manufactured in the liver and peculiar to the bile, do not accumulate in the blood when the function of the liver is interfered with, and are, in short, products of *secretion*. But it has another function connected with depuration, which is dependent on the presence of the cholesterine, which is an *excretion*. The flow of the bile is remittent, being much increased during the digestive act, but produced during the intervals of digestion, for the purpose of separating the cholesterine from the blood which is constantly receiving it.

5. The ordinary normal feces do not contain cholesterine, but contain *stercorine* (formerly called seroline, from its being supposed to exist only in the serum of the blood), produced by a transformation of the cholesterine of the bile during the digestive act.

6. The change of cholesterine into stercorine does not take place when digestion is arrested, or before this process commences; consequently, stercorine is not found in the meconium, or in the feces of hibernating animals during their torpid condition. These matters contain cholesterine in large abundance, which also sometimes appears in the feces of animals after a prolonged fast. Stercorine is the form in which cholesterine is discharged from the body.

7. The difference between the two varieties of jaundice with which we are familiar, the one characterized only by yellowness of the skin, and comparatively innocuous, while the other is attended with very grave symptoms, and is almost invariably fatal, is dependent upon the obstruction of the bile in the one case, and its suppression in the other. In the first instance, the bile is confined in the excretory passages, and its colouring matter is absorbed, while in the other, the cholesterine is retained in the blood, and acts as a poison.

8. There is a condition of the blood dependent upon the accumulation of cholesterine which I have called *Cholesteremia*. This only occurs when there is structural change in the liver, which incapacitates it from performing its excretory functions. It is characterized by symptoms of a grave character, referable to the brain, and dependent upon the poisonous effects of the retained cholesterine on this organ. It occurs with or without jaundice.

9. Cholesteremia does not occur in every instance of structural disease of the liver. Enough of the liver must be destroyed to prevent the due elimination of the cholesterine. In cases in which the organ is but moderately affected, the sound portion is capable of performing the eliminative function of the whole.

10. In cases of simple jaundice, when the feces are decolorized and the bile is entirely shut off from the intestine, stercorine is not found in the evacuations; but in cases of jaundice with cholesteremia, the stercorine may be found, though always very much diminished in quantity, showing that there is an insufficiency in the separation of the cholesterine from the blood, though its excretion is not entirely suspended. After death, but a small quantity of bile is found in the gall-bladder.

In concluding, I beg leave to express my acknowledgments to my assistant, Mr. Henry E. Paine, of Providence, R. I., one of the residents of the Bellevue Hospital, who has assisted me indefatigably in the analyses and experiments which form the basis of this paper; and to whose intelligent aid I am greatly indebted for the amount of labour which I was enabled to accomplish in a comparatively short time. This aid, with the advantages of the great hospital at Blackwell's Island, which was laid under contribution for the pathological observations, enabled me to carry on a portion of the analyses uninterruptedly for about two months.

EXPLANATION OF THE PLATES.

Fig. 1.—Cholesterine extracted from the meconium. $\frac{4}{10}$ inch objective.

Fig. 2.—Stercorine and fatty matters from the blood of the carotid artery. $\frac{1}{12}$ inch objective.

Fig. 3.—Cholesterine and small broken crystals of stercorine from the same specimen of blood from the carotid, examined eleven days after. Nachet, No. 3 objective.

Fig. 4.—Cholesterine from the brain. $\frac{1}{6}$ inch objective.

Fig. 5.—Cholesterine from the blood of the internal jugular, with a few needles of stercorine. $\frac{1}{6}$ inch objective.

Fig. 6.—Cholesterine and stercorine from the same extract as Fig. 5, examined the next day. $\frac{1}{2}$ inch objective.

Fig. 7.—Cholesterine and stercorine from the blood of the vena cava. $\frac{1}{6}$ inch objective.

Fig. 8.—Cholesterine from the blood of the portal vein. $\frac{1}{2}$ inch objective.

Fig. 9.—Cholesterine from the blood of the hepatic artery. $\frac{1}{2}$ inch objective.

Fig. 10.—Cholesterine and stercorine from the blood of the hepatic artery. $\frac{1}{2}$ inch objective.

Fig. 11.—Fatty substances from the blood of the hepatic vein. $\frac{1}{12}$ inch objective.

Fig. 12.—Cholesterine and stercorine from the same specimen, examined the following day. $\frac{1}{2}$ inch objective.

Fig. 13.—Cholesterine extracted from the bile. $\frac{1}{6}$ inch objective.

Fig. 14.—Stercorine from the human feces. $\frac{4}{10}$ inch objective.

Fig. 15.—Stercorine from the same specimen, after it had been melted, placed on a glass slide, covered with thin glass, and allowed to crystallize. The crystallization was very slow, occupying some weeks. This Fig. shows the splitting up of the borders and points of the crystals with the globules referred to on page 36. The globules were of variable size, and some of them were arranged in rows, which, with an inferior glass, might have been mistaken for varicosities on the needles. From their appearance in this specimen, after it had been so thoroughly purified, I am inclined to change the opinion expressed page 36, and regard them as composed of stercorine and not fatty impurities. $\frac{1}{6}$ inch objective.